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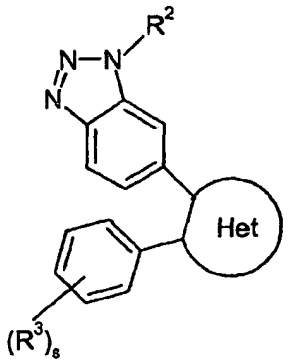
(54) Novel benzotriazoles anti-inflammatory compounds

(57) The present invention relates to novel benzotriazoles of the formula I



I

wherein Het is an optionally substituted 5-membered heterocycle containing one to two heteroatoms selected from nitrogen, sulfur and oxygen wherein at least one of said heteroatoms atoms must be nitrogen;

R^2 is selected from the group consisting of hydrogen, $(C_1\text{-}C_6)$alkyl or other suitable substituents;
R^3 is selected from the group consisting of hydrogen, $(C_1\text{-}C_6)$alkyl or other suitable substituents;
s is an integer from 0-5;
to intermediates for their preparation, to pharmaceutical compositions containing them and to their medicinal use. The compounds of the present invention are potent inhibitors of MAP kinases, preferably p38 kinase. They are useful in the treatment of inflammation, osteoarthritis, rheumatoid arthritis, cancer, repurfusion or ischemia in stroke or heart attack, autoimmune diseases and other disorders.

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Descripti n

[0001] The present invention relates to novel benzotriazoles, to intermediates for their preparation, to pharmaceutical compositions containing them and to their medicinal use. The compounds of the present invention are potent inhibitors of MAP kinases, preferably p38 kinas . They ar useful in the treatment of inflammation, osteoarthritis, rhematoid arthritis, cancer, reperfusion or ischemia in stroke or heart attack, autoimmune diseases and other disorders.

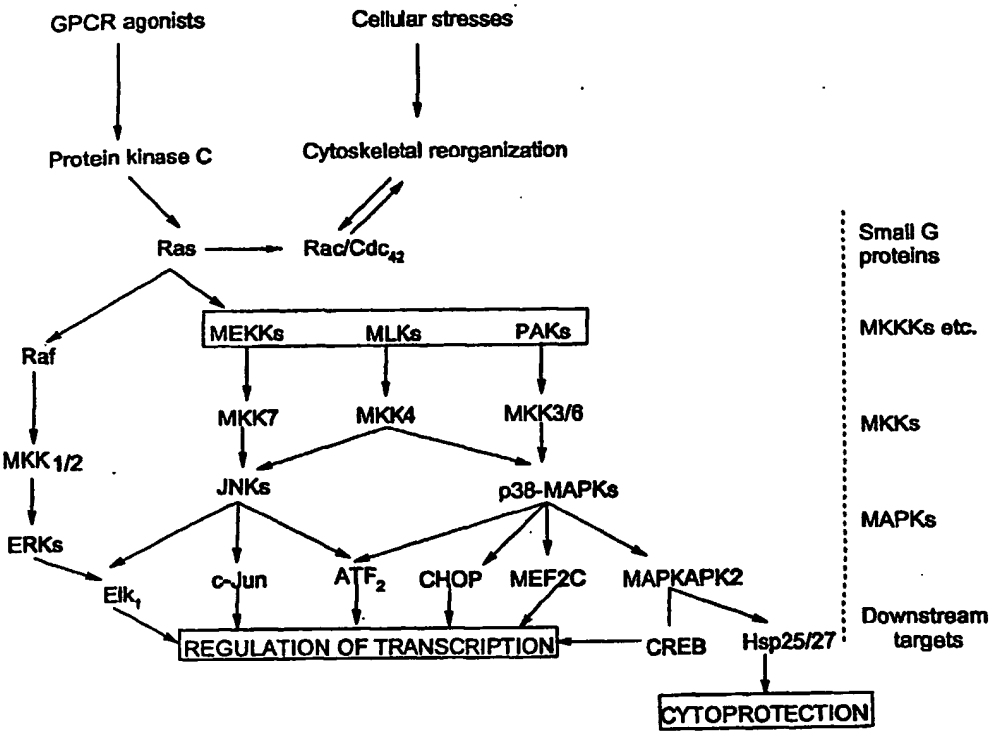
[0002] Intracellular signal transduction is the means by which cells respond to extracellular stimuli. Regardless of the nature of the cell surface receptor (e. g. protein tyrosine kinase or seven-transmembrane G-protein coupled), protein kinases and phosphatases along with phopholipases are the essential machinery by which the signal is further transmitted within the cell [Marshall, J.C. Cell , 80, 179-278 (1995)]. Protein kinases can be categorized into five classes with the two major classes being, tyrosine kinases and serine / threonine kinases depending upon whether the enzyme phosphorylates its substrate(s) on specific tyrosine(s) or serine / threonine(s) residues [Hunter, T. Methods in Enzymology (Protein Kinase Classification) p. 3, Hunter, T.; Sefton, B. M.; eds. vol. 200, Academic Press; San Diego, 1991].

[0003] For most biological responses, multiple intracellular kinases are involved and an individual kinase can be involved in more than one signaling pathway. These kinases are often cytosolic and can translocate to the nucleus or the ribosomes where they can affect transcriptional and translational events, respectively. The involvement of kinases in transcriptional control is presently much better understood than their effect on translation as illustrated by the studies on growth factor induced signal transduction involving MAP/ERK kinase [Marshall, C.J. Cell, 80, 179 (1995); Herskowitz, I. Cell, 80, 187 (1995); Hunter, T. Cell, 80, 225 (1995); Seger, R., and Krebs, E.G. FASEB J., 726-735 (1995)].

[0004] While many signaling pathways are part of normal cell homeostasis, numerous cytokines (e.g., IL-1 and TNF) and certain other mediators of inflammation (e.g., COX-2, and iNOS) are produced only as a response to stress signals such as bacterial lipopolysaccharide (LPS). Early evidence suggesting that the signal transduction pathway leading to LPS-induced cytokine biosynthesis involved protein kinases came from studies of Weinstein [Weinstein, et al., J. Immunol 151, 3829(1993)] but the specific protein kinases involved were not identified. Working from a similar perspective, Han [Han, et al., Science 265, 808(1994)] identified murine p38 as a kinase which is tyrosine phosphorylated in response to LPS. Additional evidence of the involvement of the p38 kinase in LPS-stimulated signal transduction pathway leading to the initiation of proinflammatory cytokine biosynthesis was provided by the discovery of p38 kinase (CSBP 1 and 2) by Lee [Lee; et al,. Nature, 372, 739(1994)] as the molecular target for a novel class of anti-inflammatory agents. Thus, compounds which inhibit p38 will inhibit IL-1 and TNF synthesis in human monocytes. Such results have been reported by [Lee, et al., Int. J. Immunopharmac. 10(7), 835(1988)] and [Lee; et al., Annals N.Y. Acad. Sci., 696, 149(1993)].

FIGURE 1

MAP Kinase Family: General Feature



[0005] It is now accepted that CSBP/p38 is a one of several kinases involved in a stress-response signal transduction pathway which is parallel to and largely independent of the analogous mitogen-activated protein kinase cascade (Figure 1). Stress signals, including LPS, pro-inflammatory cytokines, oxidants, UV light and osmotic stress, activate kinases upstream from CSBP/p38 which in turn phosphorylate CSBP/p38 at threonine 180 and tyrosine 182 resulting in CSBP/p38 activation. MAPKAP kinase-2 and MAPKAP kinase-3 have been identified as downstream substrates of CSBP/p38 which in turn phosphorylate heat shock protein Hsp 27. It is now known that MAPKAP-2 is essential for LPS induced TNFα biosynthesis [Kotlyarov et al. Nature Cell Biol., 1, 94 (1999), see also Cohen, P. Trends Cell Biol., 353-361(1997)].

[0006] In addition to inhibiting IL-1 and TNF, CSBP/p38 kinase inhibitors also decrease the synthesis of a wide variety of pro-inflammatory proteins including, IL-6, IL-8, GM-CSF and COX-2. Inhibitors of CSBP/p38 kinase have also been shown to suppress the TNF-induced expression of VCAM-1 on endothelial cells, the TNF-induced phosphorylation and activation of cytosolic PLA2 and the IL-1 stimulated synthesis of collagenase and stromelysin. These and additional data demonstrate that CSBP/p38 is involved not only cytokine synthesis, but also in cytokine signaling [CSBP/p38 kinase reviewed in Cohen, P. Trends Cell Biol., 353-361 (1997)].

[0007] Interleukin-1 (IL-1) and Tumor Necrosis Factor (TNF) are biological substances produced by a variety of cells, such as monocytes or macrophages. IL-1 has been demonstrated to mediate a variety of biological activities thought to be important in immunoregulation and other physiological conditions such as inflammation [See, e.g,. Dinarello et al., Rev. Infect. Disease, 6, 51 (1984)]. The myriad of known biological activities of IL-1 include the activation of T helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, induction of acute phase proteins and the suppression of plasma iron levels.

[0008] There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These disease states include rheumatoid arthritis, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease, tuberculosis, atherosclerosis, muscl degeneration, cachexia, psoriatic arthritis and Reiter's syndrome; gout, traumatic arthritis, rubella arthritis, and acute synovitis. Recent evidence also links IL-1 activity to diabetes and pancreatic β cell disfunction, Dinarello, J. Clinical Immunology, 5 (5), 287-297 (1985).

[0009] Excessive or unregulated TNF production has been implicat d in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, f ver and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, or ARC (AIDS related complex), keloid information, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis.

[0010] Interleukin-8 (IL-8) is a chemotactic factor produced by several cell types including mononuclear cells, fibroblasts, endothelial cells, and keratinocytes. Its production from endothelial cells is induced by IL-1. TNF, or lipopolysaccharide (LPS). IL-8 stimulates a number of functions *in vitro*. It has been shown to have chemoattractant properties for neutrophils, T-lymphocytes, and basophils. In addition it induces histamine release from basophils from both normal and atopic individuals as well lysozomal enzyme release and respiratory burst from neutrophils. IL-8 has also been shown to increase the surface expression of Mac-1 (CD11b/CD18) on neutrophils without *de novo* protein synthesis, this may contribute to increased adhesion of the neutrophils to vascular endothelial cells. Many diseases are characterized by massive neutrophil infiltration. Conditions associated with an increase in IL-8 production (which is responsible for chemotaxis of neutrophils into the inflammatory site) would benefit by compounds which are suppressive of IL-8 production.

[0011] IL-1 and TNF affect a wide variety of cells and tissues and these cytokines as well as other leukocyte derived cytokines are important and critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these cytokines is of benefit in controlling, reducing and alleviating many of these disease states.

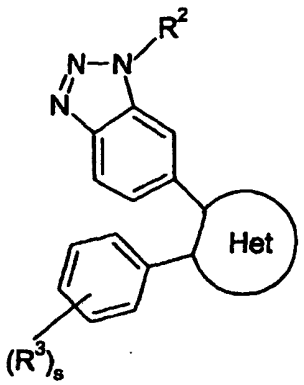
[0012] Inhibition of signal transduction via CSBP/p38, which in addition to IL-1, TNF and IL-8 described above is also required for the synthesis and/or action of several additional pro-inflammatory proteins (i.e., IL-6, GM-CSF, COX-2, collagenase and stromelysin), is expected to be a highly effective mechanism for regulating the excessive and destructive activation of the immune system. This expectation is supported by the potent and diverse anti-inflammatory activities described for CSBP/p38 kinase inhibitors [Badger, et al., J. Pharm. Exp. Thera. 279 (3); 1453-1461. (1996); Griswold, et al., Pharmacol. Comm., 7, 323-229 (1996)].

[0013] There remains a need for treatment, in this field, for compounds which are cytokine suppressive anti-inflammatory drugs, i.e., compounds which are capable of inhibiting the CSBP/p38/RK kinase.

[0014] CSBP/p38/RK kinase inhibitors are well known to those skilled in the art. International Patent Publication WO 00/40243, published July 13, 2000, refers to pyridine substituted pyridine compounds and states that these compounds are p38 inhibitors. International Patent Publication WO 00/63204, published October 26, 2000, refers to substituted azole compounds and states that these compounds are p38 inhibitors. International Patent Publication WO 00/31065, published June 2, 2000, refers to certain heterocyclic compounds and states that these compounds are p38 inhibitors. International Patent Publication WO 00/06563, published February 10, 2000, refers to substituted imidazole compounds and states that these compounds are p38 inhibitors. International Patent Publication WO 00/41698, published July 20, 2000, refers to certain ω-carboxy aryl substituted diphenyl urea compounds and states that these compounds are p38 inhibitors. United States Patent 5,716,955 refers to certain substituted imidazole compounds and states that these compounds are p38 inhibitors. United States Patent 5,716,972 refers to certain pyridinyl substituted imidazole compounds and states that these compounds are p38 inhibitors. United States Patent 5,717,100 refers to certain pyridinyl substituted imidazole compounds and states that these compounds are p38 inhibitors. United States Patent 5,756,499 refers to certain substituted imidazole compounds and states that these compounds are p38 inhibitors. United States Provisional Applications 60/274791 and 60/274840, both filed March 9, 2001, refer to benzimidazolone and triazolopyridine p38 inhibitors, respectively.

SUMMARY OF THE INVENTION

[0015] The present invention relates to a compound of the formula



I

wherein

Het is an optionally substituted 5-membered heteroaryl containing one or two heteroatoms selected from nitrogen, sulfur and oxygen wherein at least one of said heteroatoms atoms must be nitrogen;
R^2 is selected from the group consisting of hydrogen, (C_1-C_6)alkyl or other suitable substituents;
R^3 is selected from the group consisting of hydrogen, (C_1-C_6)alkyl or other suitable substituents; and
s is an integer from zero to five;

and pharmaceutically acceptable salts and prodrugs thereof.

[0016] The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts.

[0017] The invention also relates to base addition salts of formula I. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those compounds of formula I that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as *N*-methylglucamine-(meglumine), *and the lower alkanolammonium and other base salts of pharmaceutically acceptable* organic amines.

[0018] *The compounds of this invention include all stereoisomers* (e.g., cis and trans isomers) and all optical isomers of compounds of the formula I (e.g., R and S enantiomers), as well as racemic, diastereomeric and other mixtures of such isomers.

[0019] The compounds, salts and prodrugs of the present invention can exist in several tautomeric forms, including the enol and imine form, and the keto and enamine form and geometric isomers and mixtures thereof. All such tautomeric forms are included within the scope of the present invention. Tautomers exist as mixtures of a tautomeric set in solution. In solid form, usually one tautomer predominates. Even though one tautomer may be described, the present invention includes all tautomers of the present compounds.

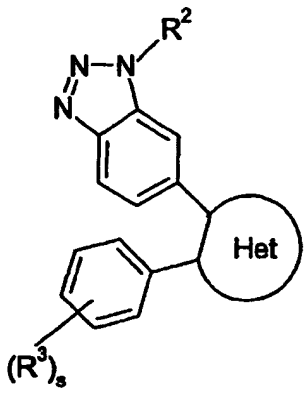
[0020] The present invention also includes atropisomers of the present invention. Atropisomers refer to compounds of formula I that can be separated into rotationally restricted isomers.

[0021] The compounds of this invention may contain olefin-like double bonds. When such bonds are present, the compounds of the invention exist as *cis and trans configurations and as mixtures thereof.*

[0022] A "suitable substituent" is intended to mean a chemically and pharmaceutically acceptable functional group *i.e., a moiety that does not negate the inhibitory activity of the inventive compounds. Such suitable substituents may* be routinely selected by those skilled in the art. Illustrative examples of suitable substituents include, but are not limited to halo groups, perfluoroalkyl groups, perfluoroalkoxy groups, alkyl groups, alkenyl groups, alkynyl groups, hydroxy groups, oxo groups, mercapto groups, alkylthio groups, alkoxy groups, aryl or heteroaryl groups, aryloxy or heteroaryloxy groups, aralkyl or heteroaralkyl groups, aralkoxy or heteroaralkoxy groups, HO-(C=O)- groups, amino groups, alkyl- and dialkylamino groups, carbamoyl groups, alkylcarbonyl groups, alkoxycarbonyl groups, alkylaminocarbonyl

groups dialkylamino carbonyl groups, arylcarbonyl groups, aryloxycarbonyl groups, alkylsulfonyl groups, arylsulfonyl groups and the like. Those skilled in the art will appreciate that many substituents can be substituted by additional substituents.

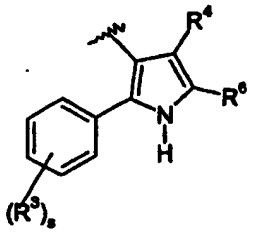
[0023] More specifically, the present invention also relates to a compound of th formula



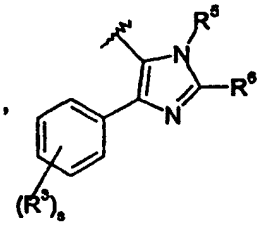
I

wherein

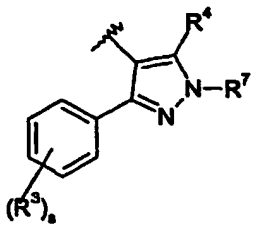
Het is an optionally substituted 5-membered heteroaryl which taken together with $(R^{3-})_s$ phenyl is selected from the group consisting of



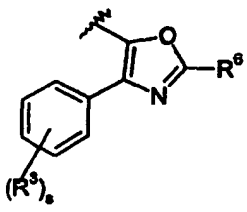
(a)



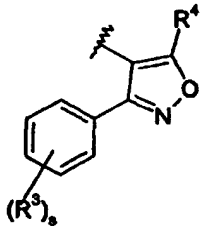
(b)



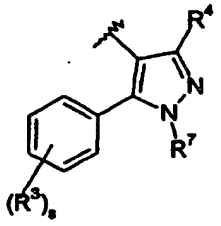
(c)



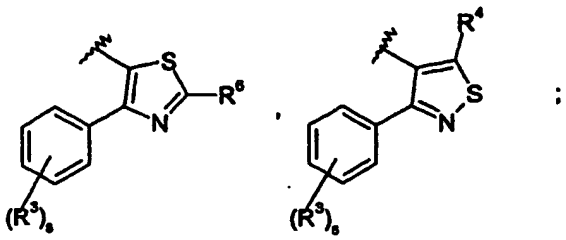
(d)



(e)



(f)



(g) (h)

R^2 is selected from the group consisting of hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, phenyl, $(C_1\text{-}C_{10})$heteroaryl and $(C_1\text{-}C_{10})$heterocyclic; wherein each of the aforesaid $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, phenyl, $(C_1\text{-}C_{10})$heteroaryl and $(C_1\text{-}C_{10})$heterocyclic substituents may optionally be independently substituted by one to four moieties independently selected from the group consisting of halo, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, perhalo $(C_1\text{-}C_6)$alkyl, phenyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_{10})$heteroaryl, $(C_1\text{-}C_{10})$heterocyclic, formyl, -CN, $(C_1\text{-}C_6)$alkyl-(C=O)-, phenyl-(C=O)-, HO-(C=O)-, $(C_1\text{-}C_6)$alkyl-O-(C=O)-, $(C_1\text{-}C_6)$alkyl-NH-(C=O)-, $[(C_1\text{-}C_6)$alkyl$]_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[$((C_1\text{-}C_6)$alkyl)-N]-(C=O)-, $-NO_2$, amino, $(C_1\text{-}C_6)$alkylamino, $[(C_1\text{-}C_6)$alkyl$]_2$-amino, $(C_1\text{-}C_6)$alkyl-(C=O)-NH-, $(C_1\text{-}C_6)$alkyl-(C=O)-[$((C_1\text{-}C_6)$alkyl)-N]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[$((C_1\text{-}C_6)$alkyl)-N]-, H_2N-(C=O)-NH-, $(C_1\text{-}C_6)$alkyl-HN-(C=O)-NH-, $[(C_1\text{-}C_6)$alkyl-$]_2$N-(C=O)-NH-, $(C_1\text{-}C_6)$alkyl-HN-(C=O)-[$((C_1\text{-}C_6)$alkyl)-N]-, $[(C_1\text{-}C_6)$alkyl-$]_2$N-(C=O)-[$((C_1\text{-}C_6)$alkyl)-N]-, phenyl-HN-(C=O)-NH-, (phenyl-$)_2$N-(C=O)-NH-, phenyl-HN-(C=O)-[$((C_1\text{-}C_6)$alkyl)-N]-, (phenyl-$)_2$N-(C=O)-[$((C_1\text{-}C_6)$alkyl)-N]-, $(C_1\text{-}C_6)$alkyl-O-(C=O)-NH-, $(C_1\text{-}C_6)$alkyl-O-(C=O)-[$((C_1\text{-}C_6)$alkyl)-N]-, phenyl-O-(C=O)-NH-, phenyl-O-(C=O)-[$((C_1\text{-}C_6)$alkyl)-N]-, $(C_1\text{-}C_6)$alkyl-SO_2NH-, phenyl-SO_2NH-, $(C_1\text{-}C_6)$alkyl-SO_2-, phenyl-SO_2-, hydroxy, $(C_1\text{-}C_6)$alkoxy, perhalo $(C_1\text{-}C_6)$alkoxy, phenoxy, $(C_1\text{-}C_6)$alkyl-(C=O)-O-, phenyl-(C=O)-O-, H_2N-(C=O)-O-, $(C_1\text{-}C_6)$alkyl-HN-(C=O)-O-, $[(C_1\text{-}C_6)$alkyl-$]_2$N-(C=O)-O-, phenyl-HN-(C=O)-O-, and (phenyl-$)_2$N-(C=O)-O-; wherein two adjacent R^2 substituents on said $(C_3\text{-}C_{10})$cycloalkyl, phenyl, $(C_1\text{-}C_{10})$heteroaryl or $(C_1\text{-}C_{10})$heterocyclic may be taken together with the carbon or heteroatom to which they are attached to form a five to six membered carbocyclic or heterocyclic ring; wherein each of said moieties containing a phenyl alternative may optionally be substituted by one or two radicals independently selected from the group consisting of $(C_1\text{-}C_6)$alkyl, halo, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl and perhalo$(C_1\text{-}C_6)$alkoxy;

each R^3 is independently selected from the group consisting of halo, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, perhalo$(C_1\text{-}C_6)$alkyl, phenyl, $(C_1\text{-}C_{10})$heteroaryl, $(C_1\text{-}C_{10})$heterocyclic, $(C_3\text{-}C_{10})$cycloalkyl, hydroxy, $(C_1\text{-}C_6)$alkoxy, perhalo$(C_1\text{-}C_6)$alkoxy, phenoxy, $(C_1\text{-}C_{10})$heteroaryl-O-, $(C_1\text{-}C_{10})$heterocyclic-O-, $(C_3\text{-}C_{10})$cycloalkyl-O-, $(C_1\text{-}C_6)$alkyl-S, $(C_1\text{-}C_6)$alkyl-SO_2-, $(C_1\text{-}C_6)$alkyl-NH-SO_2-, $-NO_2$, amino, $(C_1\text{-}C_6)$alkylamino, $[(C_1\text{-}C_6)$alkyl$]_2$-amino, $(C_1\text{-}C_6)$alkyl-SO_2-NH-, $(C_1\text{-}C_6)$alkyl-(C=O)-NH-, $(C_1\text{-}C_6)$alkyl-(C=O)-[$((C_1\text{-}C_6)$alkyl)-N]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[$((C_1\text{-}C_6)$alkyl)-N]-, -CN, $(C_1\text{-}C_6)$alkyl-(C=O)-, phenyl-(C=O)-, $(C_1\text{-}C_{10})$heteroaryl-(C=O)-, $(C_1\text{-}C_{10})$heterocyclic-(C=O)-, $(C_3\text{-}C_{10})$cycloalkyl-(C=O)-, HO-(C=O)-, $(C_1\text{-}C_6)$alkyl-O-(C=O)-, H_2N(C=O)-, $(C_1\text{-}C_6)$alkyl-NH-(C=O)-, $[(C_1\text{-}C_6)$alkyl$]_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[$((C_1\text{-}C_6)$alkyl)-N]-(C=O)-, $(C_1\text{-}C_{10})$heteroaryl-NH-(C=O)-, $(C_1\text{-}C_{10})$heterocyclic-NH-(C=O)-, $(C_3\text{-}C_{10})$cycloalkyl-NH-(C=O)- and $(C_1\text{-}C_6)$alkyl-(C=O)-O-; wherein two adjacent R^3 substituents may optionally be taken together to form a three to six membered carbocyclic or heterocyclic ring;

s is an integer from zero to five;

R^4 and R^6 are each independently selected from the group consisting of hydrogen, halo and R^9-B-$(CH_2)_n$-;

n is an integer from zero to six;

each B is independently a bond, -(CHR^{10})-, -O-, -S-, -(SO_2)-, -(C=O)-, -O(C=O)-, -(C=O)-O-, -(C=O)-NR^{10}-, -(R^{10}-N)-, -(R^{10}-N)-SO_2-, -(R^{10}-N)-(C=O)-, -SO_2-(NR^{10})-, -(R^{10}-N)-(C=O)-(NR^{11})-, -(O)-(C=O)-(NR^{10})- or -(R^{10}-N)-(C=O)-O-;

R^5 and R^7 are each independently selected from the group consisting of hydrogen, R^{14}-($CR^{15}H)_p$-, phenyl, $(C_1\text{-}C_{10})$heteroaryl, $(C_1\text{-}C_{10})$heterocyclic, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_6)$alkyl-(SO_2)-, phenyl-(SO_2)-, H_2N-(SO_2)-, $(C_1\text{-}C_6)$alkyl-NH-(SO_2)-, $[(C_1\text{-}C_6)$alkyl-$]_2$N-(SO_2)-, phenyl-NH-(SO_2)-, (phenyl-$)_2$N-(SO_2)-, R^{16}-$(C_1\text{-}C_6)$alkyl-(C=O)-, phenyl-(C=O)-, $(C_1\text{-}C_{10})$heteroaryl-(C=O)-, $(C_1\text{-}C_{10})$heterocyclic-(C=O)-, $(C_3\text{-}C_{10})$cycloalkyl-(C=O)-, $(C_1\text{-}C_6)$alkyl-O-(C=O)-, $(C_1\text{-}C_{10})$heterocyclic-O-(C=O)-, $(C_3\text{-}C_{10})$cycloalkyl-O-(C=O)-, H_2N-(C=O)-, $(C_1\text{-}C_6)$alkyl-NH-(C=O)-, phenyl-NH-(C=O)-, $(C_1\text{-}C_{10})$heteroaryl-NH-(C=O)-, $(C_1\text{-}C_{10})$heterocyclic-NH-(C=O)-, $(C_3\text{-}C_{10})$cycloalkyl-NH-(C=O)-, $[(C_1\text{-}C_6)$alkyl-$]_2$N-(C=O)-, (phenyl-$)_2$N-(C=O)-, phenyl-[$((C_1\text{-}C_6)$alkyl)-N]-(C=O)-, $(C_1\text{-}C_{10})$heteroaryl-($((C_1\text{-}C_6)$alkyl)-N]-(C=O)-, $(C_1\text{-}C_{10})$heterocyclic-[$((C_1\text{-}C_6)$alkyl)-N]-(C=O)-, and $(C_3\text{-}C_{10})$cycloalkyl-[$((C_1\text{-}C_6)$alkyl)-N]-(C=O)-, wherein each of the aforesaid phenyl, heterocyclic, heteroaryl or cycloalkyl R^5 and R^7 alternatives

may optionally be independently substituted by one to four moieties independently selected from the group consisting of halo, R^{16}-(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, phenyl, benzyl, (C_1-C_{10})heterocyclic, (C_1-C_{10})heteroaryl, (C_1-C_6)alkyl-SO_2-, formyl, -CN, (C_1-C_6)alkyl-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, (C_3-C_{10})cycloalkyl-O-(C=O)-, (C_1-C_{10})heterocyclic-O-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, phenyl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, (C_3-C_{10})cycloalkyl-O-, phenoxy, (C_1-C_{10})heterocyclic-O-, (C_1-C_{10})heteroaryl-O-, (C_1-C_6)alkyl-(C=O)-O-, (C_3-C_{10})cycloalkyl-(C=O)-O-, phenyl-(C=O)-O-, (C_1-C_{10})heterocyclic-(C=O)-O-, (C_1-C_{10})heteroaryl-(C=O)-O-, -NO_2, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, formamidyl, (C_1-C_6)alkyl-(C=O)-NH-, (C_3-C_{10})cycloalkyl-(C=O)-NH-, phenyl-(C=O)-NH-, (C_1-C_{10})heterocyclic-(C=O)-NH-, (C_1-C_{10})heteroaryl-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-[(C_1-C_6)alkyl-N]-, (C_1-C_6)alkyl-SO_2NH-, (C_3-C_{10})cycloalkyl-SO_2NH-, phenyl-SO_2NH-, (C_1-C_{10})heterocyclic-SO_2NH- and (C_1-C_{10})heteroaryl-SO_2NH-; wherein each of said phenyl and heteroaryl moiety alternatives may optionally be substituted by one or two radicals independently selected from halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_6)alkyl and perfluoro(C_1-C_6)alkoxy;

p is an integer from one to six;

R^9 is selected from the group consisting of hydrogen, -CF_3, -C≡N, R^{13}-($R^{12}CH$)$_m$-, phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic and (C_3-C_{10})cycloalkyl; wherein each of the aforesaid R^9 phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic and (C_3-C_{10})cycloalkyl substituents may optionally be substituted by one to four moieties independently selected from the group consisting of halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic, (C_3-C_{10})cycloalkyl, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, phenoxy, (C_1-C_{10})heteroaryl-O-, (C_1-C_{10})heterocyclic-O-, (C_3-C_{10})cycloalkyl-O-, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-NH-SO_2-, -NO_2, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, (C_1-C_6)alkyl-SO_2-NH-, (C_1-C_6)alkyl-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[((C_1-C_6)alkyl)-N]-, -CN, (C_1-C_6)alkyl-(C=O)-; phenyl-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, (C_1-C_6)alkyl-(C=O)-O- and phenyl-(C=O)-O-; wherein two adjacent moieties on said R^9 phenyl, (C_1-C_{10})heterocyclic or (C_3-C_{10})cycloalkyl substituents may be taken together with the carbon or heteroatom to which they are attached to form a five to six membered heterocyclic or carbocyclic ring;

m is an integer from one to six;

R^{10} is hydrogen, (C_1-C_6)alkyl-SO_2- or (C_1-C_6)alkyl;

R^{11} is hydrogen or (C_1-C_6)alkyl;

each R^{12} is independently selected from the group consisting of hydrogen, amino, (C_1-C_6)alkoxy or (C_1-C_6)alkyl;

R^{13} is selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic, (C_3-C_{10})cycloalkyl, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, phenoxy, (C_1-C_{10})heteroaryl-O-, (C_1-C_{10})heterocyclic-O-, (C_3-C_{10})cycloalkyl-O-, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-NH-SO_2-, -NO_2, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, (C_1-C_6)alkyl-SO_2-NH-, phenyl-SO_2-NH-, (C_1-C_6)alkyl-SO_2-[((C_1-C_6)alkyl)-N]-, phenyl-SO_2-[((C_1-C_6)alkyl)-N]-, (C_1-C_6)alkyl-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[((C_1-C_6)alkyl)-N]-, -CN, (C_1-C_6)alkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, (C_1-C_6)alkyl-(C=O)-O- and phenyl-(C=O)-O-;

R^{14} is selected from the group consisting of hydrogen, halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, phenyl, (C_1-C_{10})heterocyclic, (C_1-C_{10})heteroaryl, phenyl-(S=O)-, (C_1-C_6)alkyl-SO_2-, phenyl-SO_2-, H_2N-SO_2-, (C_1-C_6)alkyl-NH-SO_2-, phenyl-NH-SO_2-, [(C_1-C_6)alkyl-]$_2$N-SO_2-, (phenyl-)$_2$N-SO_2-, formyl, -CN, (C_1-C_6)alkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, HO-(C=O)-, R^{16}-(C_1-C_6)alkyl-O-(C=O)-, (C_3-C_{10})cycloalkyl-O-(C=O)-, (C_1-C_{10})heterocyclic-O-(C=O)-, H_2N-(C=O)-, R^{16}-(C_1-C_6)alkyl-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, phenyl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_1-C_{10})heteroaryl-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_1-C_{10})heterocyclic-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_3-C_{10})cycloalkyl-[((C_1-C_6)alkyl)-N]-(C=O)-, hydroxy, R^{16}-(C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, (C_3-C_{10})cycloalkyl-O-, phenoxy, (C_1-C_{10})heterocyclic-O-, (C_1-C_{10})heteroaryl-O-, R^{16}-(C_1-C_6)alkyl-(C=O)-O-, (C_3-C_{10})cycloalkyl-(C=O)-O-, phenyl-(C=O)-O-, (C_1-C_{10})heterocyclic-(C=O)-O-, (C_1-C_{10})heteroaryl-(C=O)-O-, -NO_2, amino, R^{16}-(C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, formamidyl, R^{16}-(C_1-C_6)alkyl-(C=O)-NH-, (C_3-C_{10})cycloalkyl-(C=O)-NH-, phenyl-(C=O)-NH-, (C_1-C_{10})heterocyclic-(C=O)-NH-, (C_1-C_{10})heteroaryl-(C=O)-NH-,

R^{16}-(C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-[((C_1-C_6)alkyl)-N]-, R^{16}-(C_1-C_6)alkyl-SO_2NH-, (C_3-C_{10})cycloalkyl-SO_2NH-, phenyl-SO_2NH-, (C_1-C_{10})heterocyclic-SO_2NH- and (C_1-C_{10})heteroaryl-SO_2NH-; wherein each of the aforesaid phenyl, heterocyclic, heteroaryl or cycloalkyl R^{14} alternatives may optionally be independently substituted by one to four moieties independently selected from the group consisting of halo, R^{16}-(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, phenyl, benzyl, (C_1-C_{10})heterocyclic, (C_1-C_{10})heteroaryl, (C_1-C_6)alkyl-SO_2-, formyl, -CN, R^{16}-(C_1-C_6)alkyl-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, (C_3-C_{10})cycloalkyl-O-(C=O)-, (C_1-C_{10})heterocyclic-O-(C=O)-, (C_1-C_{10})heteroaryl-O-(C=O)-, H_2N-(C=O)-, R^{16}-(C_1-C_6)alkyl-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, phenyl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, hydroxy, R^{16}-(C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, (C_3-C_{10})cycloalkyl-O-, phenoxy, (C_1-C_{10})heterocyclic-O-, (C_1-C_{10})heteroaryl-O-, R^{16}-(C_1-C_6)alkyl-(C=O)-O-, (C_3-C_{10})cycloalkyl-(C=O)-O-, phenyl-(C=O)-O-, (C_1-C_{10})heterocyclic-(C=O)-O-, (C_1-C_{10})heteroaryl-(C=O)-O-, -NO_2, amino, R^{16}-(C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, formamidyl, R^{16}-(C_1-C_6)alkyl-(C=O)-NH-, (C_3-C_{10})cycloalkyl-(C=O)-NH-, phenyl-(C=O)-NH-, (C_1-C_{10})heterocyclic-(C=O)-NH-, (C_1-C_{10})heteroaryl-(C=O)-NH-, R^{16}-(C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-[((C_1-C_6)alkyl)-N]-, R^{16}-(C_1-C_6)alkyl-SO_2NH-, (C_3-C_{10})cycloalkyl-SO_2NH-, phenyl-SO_2NH-, (C_1-C_{10})heterocyclic-SO_2NH- and (C_1-C_{10})heteroaryl-SO_2NH-; wherein each of said phenyl and heteroaryl moiety alternatives may optionally be substituted by one or two radicals independently selected from the group consisting of halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_6)alkyl and perfluoro(C_1-C_6)alkoxy;

each R^{15} is independently selected from the group consisting of hydrogen, halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, perhalo(C_1-C_6)alkyl, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl-(C=O)-O-, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, formamidyl and (C_1-C_6)alkyl-(C=O)-NH-;

each R^{16} is independently selected from the group consisting of hydrogen, halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, (C_1-C_{10})heterocyclic, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, (C_1-C_6)alkyl-(C=O)-O-, -NO_2, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, formamidyl and (C_1-C_6)alkyl-(C=O)-NH-; wherein said (C_1-C_{10})heterocyclic may optionally be substituted by one to three substitutents independently selected from the group consisting of halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, amino, (C_1-C_6)alkylamino and [(C_1-C_6)alkyl]$_2$-amino;

or R^4 and R^6 or R^4 and R^7 or R^5 and R^6 may be taken together with the atoms to which they are attached to form an optionally substituted five to ten membered saturated, unsaturated or aromatic ring optionally containing two to three heteroatoms independently selected from NH, N, O, S, SO or SO_2; wherein said ring may be optionally substituted by one to three substituents independently selected from the group consisting of oxo, halo, (C_1-C_6)alkyl, phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic, (C_3-C_{10})cycloalkyl, hydroxy, (C_1-C_6)alkoxy, phenoxy, (C_1-C_{10})heteroaryl-O-, (C_1-C_{10})heterocyclic-O-, (C_3-C_{10})cycloalkyl-O-, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-SO_2-, phenyl-S-, phenyl-(S=O)-, phenyl-SO_2-, (C_1-C_6)alkyl-NH-SO_2-, [(C_1-C_6)alkyl]$_2$-N-SO_2-, phenyl-NH-SO_2-, (phenyl)$_2$-N-SO_2-, phenyl-[N(C_1-C_6)alkyl]-SO_2-, formyl, (C_1-C_6)alkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-. (C_1-C_{10})heterocyclic-O-(C=O)-, (C_3-C_{10})cycloalkyl-O-(C=O)-, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[(C_1-C_6)alkyl)-N]-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, (C_1-C_{10})heteroaryl-[(C_1-C_6)alkyl)-N]-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_1-C_{10})heterocyclic-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, (C_3-C_{10})cycloalkyl-[((C_1-C_6)alkyl)-N]-(C=O)-, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$amino, (C_1-C_6)alkyl-SO_2-NH-, phenyl-SO_2-NH-, (C_1-C_6)alkyl-SO_2-[((C_1-C_6)alkyl)-N]-, phenyl-SO_2-[((C_1-C_6)alkyl)-N]-, formamidyl, (C_1-C_6)alkyl-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[((C_1-C_6)alkyl)-N]-, (C_1-C_{10})heteroaryl-(C=O)-NH-, (C_1-C_{10})heteroaryl-(C=O)-[((C_1-C_6)alkyl)-N]-, (C_1-C_{10})heterocyclic-(C=O)-NH-, (C_1-C_{10})heterocyclic-(C=O)-[((C_1-C_6)alkyl)-N]-, (C_3-C_{10})cycloalkyl-(C=O)-NH-, (C_3-C_{10})cycloalkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, H_2N(C=O)-NH-, (C_1-C_6)alkyl-HN-(C=O)-NH-, (C_1-C_6)alkyl-HN-(C=O)-[((C_1-C_6)alkyl)-N]-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-NH-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-HN-(C=O)-NH-, phenyl-HN-(C=O)-[((C_1-C_6)alkyl)-N]-, (phenyl)$_2$-N-(C=O)-NH-, (phenyl)$_2$-N-(C=O)-[((C_1-C_6)alkyl)-N]-, (C_1-C_{10})heteroaryl-HN-(C=O)-NH-, (C_1-C_{10})heteroaryl-HN-(C=O)-[((C_1-C_6)alkyl)-N]-, [(C_1-C_{10})heteroaryl]$_2$-N-(C=O)-[((C_1-C_6)alkyl)-N]-, [(C_1-C_{10})heteroaryl]$_2$-N-(C=O)-NH-, (C_1-C_{10})heterocyclic-HN-(C=O)-NH-, (C_1-C_{10})heterocyclic-HN-(C=O)-[((C_1-C_6)alkyl)-N]-, [(C_1-C_{10})heterocyclic]$_2$-N-(C=O)-[((C_1-C_6)alkyl)-N]-, [(C_1-C_{10})heterocyclic]$_2$-N-(C=O)-NH-, (C_3-C_{10})cycloalkyl-HN-(C=O)-NH-, (C_3-C_{10})cycloalkyl-HN-(C=O)-[((C_1-C_6)alkyl)-N]-, [(C_3-C_{10})cycloalkyl]$_2$-N-(C=O)-[((C_1-C_6)alkyl)-N]-, [(C_3-C_{10})cycloalkyl]$_2$-N-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-O-, phenyl-(C=O)-O-, (C_1-C_{10})heteroaryl-(C=O)-O-, (C_1-C_{10})heterocyclic-(C=O)-O-, (C_3-C_{10})cycloalkyl-(C=O)-O-, (C_1-C_6)alkyl-NH-(C=O)-O-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-O-, phenyl-NH-(C=O)-O-, (C_1-C_{10})heteroaryl-NH-(C=O)-O-, (C_1-C_{10})heterocyclic-NH-(C=O)-O- and (C_3-C_{10})cycloalkyl-NH-(C=O)-O-;

or the pharmaceutically acceptable salts thereof.

[0024] As used h rein, the term "alkyl," as well as the alkyl moieties of other groups referred to her in (e.g., alkoxy), may be linear or branched (such as methyl, ethyl, *n*-propyl, *iso*propyl, n-butyl, *iso*-butyl, *secondary*-butyl, *tertiary*-butyl); optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, (C_1-C_6) alkoxy, (C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy or (C_1-C_6)alkyl. The phrase "each of said alkyl" as used herein refers to any of the preceding alkyl moieties within a group such alkoxy, alkenyl or alkylamino. Preferred alkyls include (C_1-C_4)alkyl, most preferably methyl and ethyl.

[0025] As used herein, the term "cycloalkyl" refers to a mono or bicyclic carbocyclic ring (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclopentenyl, cyclohexenyl, bicyclo[2.2.1]heptanyl, bicyclo[3.2.1]octanyl and bicyclo[5.2.0]nonanyl, etc.); optionally containing 1 or 2 double bonds and optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy or (C_1-C_6)alkyl.

[0026] As used herein, the term "halogen" includes fluoro, chloro, bromo or iodo or fluoride, chloride, bromide or iodide.

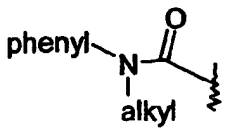
[0027] As used herein, the term "halo-substituted alkyl" refers to an alkyl radical as described above substituted with one or more halogens included, but not limited to, chloromethyl, dichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trichloroethyl, and the like; optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy or (C_1-C_6)alkyl.

[0028] As used herein, the term "alkenyl" means straight or branched chain unsaturated radicals of 2 to 6 carbon atoms, including, but not limited to ethenyl, 1-propenyl, 2-propenyl (allyl), *iso*-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, and the like; optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy or (C_1-C_6)alkyl.

[0029] As used herein, the term "(C_2-C_6)alkynyl" is used herein to mean straight or branched hydrocarbon chain radicals having one triple bond including, but not limited to, ethynyl, propynyl, butynyl, and the like; optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy or (C_1-C_6)alkyl.

[0030] As used herein, the term "carbonyl" or "(C=O)" (as used in phrases such as alkylcarbonyl, alkyl-(C=O)- or alkoxycarbonyl) refers to the joinder of the >C=O moiety to a second moiety such as an alkyl or amino group (i.e. an amido group). Alkoxycarbonylamino (i.e. alkoxy(C=O)-NH-) refers to an alkyl carbamate group. The carbonyl group is also equivalently defined herein as (C=O). Alkylcarbonylamino refers to groups such as acetamide.

[0031] As used herein, the term "phenyl-[(C_1-C_6)alkyl)-N]-(C=O)-, " as used herein, refers to a disubstituted amide group of the formula



[0032] As used herein, the term "aryl" means aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indanyl and the like; optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy or (C_1-C_6)alkyl.

[0033] As used herein, the term "heteroaryl" refers to an aromatic heterocyclic group usually with one heteroatom selected from O, S and N in the ring. In addition to said heteroatom, the aromatic group may optionally have up to four N atoms in the ring. For example, heteroaryl group includes pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, imidazolyl, pyrrolyl, oxazolyl (e.g., 1,3-oxazolyl, 1,2-oxazolyl), thiazolyl (e.g., 1,2-thiazolyl, 1,3-thiazolyl), pyrazolyl, tetrazolyl, triazolyl (e.g., 1,2,3-triazolyl, 1,2,4-triazolyl), oxadiazolyl (e.g., 1,2,3-oxadiazolyl), thiadiazolyl (e.g., 1,3,4-thiadiazolyl), quinolyl, isoquinolyl, benzothienyl, benzofuryl, indolyl, and the like; optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy or (C_1-C_6)alkyl. Particularly preferred heteroaryl groups include oxazolyl, imidazolyl, pyridyl, thienyl, furyl, thiazolyl and pyrazolyl (these heteroaryls are most preferred of the R^4, R^5, R^6 and R^7 heteroaryls).

[0034] The term "heterocyclic" as used herein refers to a cyclic group containing 1-9 carbon atoms and 1 to 4 hetero atoms selected from N, O, S or NR'. Examples of such rings include azetidinyl, tetrahydrofuranyl, imidazolidinyl, pyrrolidinyl, piperidinyl, piperazinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, thiomorpholinyl, tetrahydrothiazinyl, tetrahydro-thiadiazinyl, morpholinyl, oxetanyl, tetrahydrodiazinyl, oxazinyl, oxaithiazinyl, indolinyl, isoindolinyl, quincuclidinyl, chromanyl, isochromanyl, benzoxazinyl, and the like. Examples of said monocyclic saturated or partially saturated ring systems are tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, imidazolidin-1-yl, imidazolidin-2-yl, imidazolidin-4-yl, pyrrolidin-

1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperazin-1-yl, piperazin-2-yl, piperazin-3-yl, 1,3-oxazolidin-3-yl, isothiazolidine, 1,3-thiazolidin-3-yl, 1,2-pyrazolidin-2-yl, 1,3-pyrazolidin-1-yl, thiomorpholin-yl, 1,2-tetrahydrothiazin-2-yl, 1,3-tetrahydrothiazin-3-yl, tetrahydrothiadiazin-yl, morpholin-yl, 1,2-tetrahydrodiazin-2-yl, 1,3-tetrahydrodiazin-1-yl, 1,4-oxazin-2-yl, 1,2,5-oxathiazin-4-yl and the like; optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, $(C_1\text{-}C_6)$alkoxy, $(C_6\text{-}C_{10})$aryloxy, trifluoromethoxy, difluoromethoxy or $(C_1\text{-}C_6)$alkyl. Preferred heterocyclics include tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl.

[0035] Alternative, as used herein refers to a substituent, group or moiety which contains as any component of the substituent, group or moiety the designated functionality. Thus the phrase "each of the aforesaid phenyl, heterocyclic, heteroaryl or cycloalkyl R^5 and R^7 alternatives" refers to the R^5 and R^7 substitutents containing a phenyl, heterocyclic, heteroaryl or cycloalkyl funtionality. In the present example the identified phenyl, heterocyclic, heteroaryl or cycloalkyl R^5 ahd R^7 substitutents are $R^{14}\text{-}(CR^{15}H)_p\text{-}$, phenyl, $(C_1\text{-}C_{10})$heteroaryl, $(C_1\text{-}C_{10})$heterocyclic, $(C_3\text{-}C_{10})$cycloalkyl, phenyl-(SO_2)-, phenyl-NH-(SO_2)-, (phenyl-)$_2$N-(SO_2)-, $R^{16}\text{-}(C_1\text{-}C_6)$alkyl-(C=O)-, phenyl-(C=O)-, $(C_1\text{-}C_{10})$heteroaryl-(C=O)-, $(C_1\text{-}C_{10})$heterocyclic-(C=O)-, $(C_3\text{-}C_{10})$cycloalkyl-(C=O)-, $(C_1\text{-}C_{10})$heterocyclic-O-(C=O)-, $(C_3\text{-}C_{10})$cycloalkyl-O-(C=O)-, phenyl-NH-(C=O)-, $(C_1\text{-}C_{10})$heteroaryl-NH-(C=O)-, $(C_1\text{-}C_{10})$heterocyclic-NH-(C=O)-, $(C_3\text{-}C_{10})$cycloalkyl-NH-(C=O)-, (phenyl-)$_2$N-(C=O)-, phenyl-[$(C_1\text{-}C_6)$alkyl)-N]-(C=O)-, $(C_1\text{-}C_{10})$heteroaryl-[$(C_1\text{-}C_6)$alkyl)-N]-(C=O)-, $(C_1\text{-}C_{10})$heterocyclic-[$(C_1\text{-}C_6)$alkyl)-N]-(C=O)-, and $(C_3\text{-}C_{10})$cycloalkyl-[$(C_1\text{-}C_6)$alkyl)-N]-(C=O)-.

[0036] Embodiment as used herein refers to specific groupings of compounds or uses into discrete subgenera. Such subgenera may be cognizable according to one particular substituent such as a specific R^2 group. Other subgenera are cognizable according to combinations of various substituents, such as all compounds wherein R^2 is methyl and R^4 is a group of the formula $R^9\text{-}B\text{-}(CH_2)_n\text{-}$ and n is zero. The phrase "in combination with each of the aforementioned embodiments" refers to combinations of the identified embodiment with each embodiment previously identified in the specification. Thus an embodiment of compounds wherein R^2 is methyl "in combination with each of the aforementioned embodiments" refers to additional embodiments comprising combinations of the R^2 methyl embodiment with each embodiment previously identified in the specification.

[0037] A preferred embodiment of the present invention is that group of compounds of formula I wherein R^2 is $(C_1\text{-}C_6)$ alkyl, more preferably $(C_1\text{-}C_5)$alkyl, more preferably $(C_1\text{-}C_4)$alkyl, more preferably methyl, ethyl, or isopropyl.

[0038] Another embodiment of the present invention is that group of compounds of formula I, wherein R^2 is optionally substituted $(C_3\text{-}C_6)$cycloalkyl, more preferably optionally substituted cyclobutyl or cyclopentyl; more preferably optionally substituted by 1 to 3 substituents selected from the group consiting of fluoro, chloro, trifluoromethyl, hydroxy, $(C_1\text{-}C_6)$alkoxy, amino, trifluoromethoxy, and $(C_1\text{-}C_6)$alkyl.

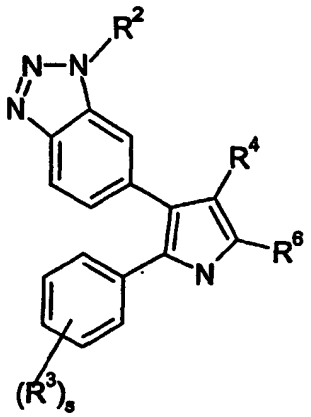
[0039] Another embodiment of the present invention is that group of compounds of formula I wherein R^2 is optionally substituted phenyl; more preferably optionally substituted by 1 to 3 substituents selected from the group consiting of fluoro, chloro, trifluoromethyl, hydroxy, $(C_1\text{-}C_6)$alkoxy, amino, trifluoromethoxy, and $(C_1\text{-}C_6)$alkyl.

[0040] Another embodiment of the present invention is that group of compounds of formula I wherein R^2 is optionally substituted $(C_1\text{-}C_{10})$heterocyclic, more preferably optionally substituted tetrahydrofuranyl, more preferably optionally substituted by 1 to 2 substituents independenty selected from the group consiting of fluoro, chloro, trifluoromethyl, hydroxy, $(C_1\text{-}C_6)$alkoxy, amino, trifluoromethoxy, and $(C_1\text{-}C_6)$alkyl.

[0041] Another embodiment of the present invention include that group of compounds of formula I wherein R^2 is optionally substituted $(C_1\text{-}C_{10})$heteroaryl, more preferably optionally substituted thiophenyl and pyridinyl, more preferably optionally substituted by 1 to 2 substituents independently selected from the group consiting of fluoro, chloro, trifluoromethyl, hydroxy, $(C_1\text{-}C_6)$alkoxy, amino, trifluoromethoxy, and $(C_1\text{-}C_6)$alkyl.

[0042] Another embodiment of the present invention is that group of compounds of formula I, wherein R^2 is hydrogen.

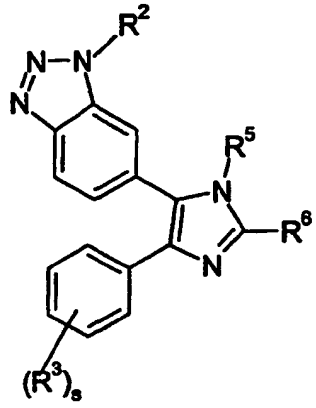
[0043] An embodiment of the present invention includes compounds of formula I, referred to as the phenyl-pyrolyl-benzotriazoles, wherein the compound has the formula



Ia

[0044] Other embodiments of the present invention include those compounds of formula I(a) in combination with each of the aforementioned embodiments of R^2.

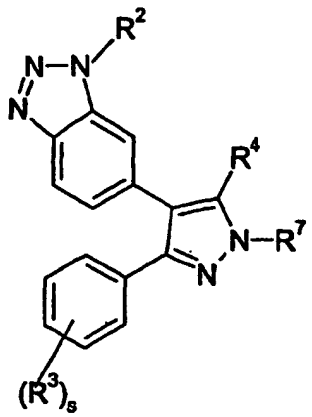
[0045] An embodiment of the present invention includes compounds of formula I, referred to as the phenyl-imidazolyl-benzotriazoles, wherein the compound has the formula



Ib

Other embodiments of the present invention include those compounds of formula I(b) in combination with each of the aforementioned embodiments of R^2.

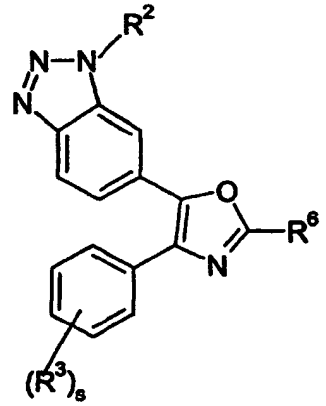
[0046] Another embodiment of the present invention includes compounds of formula I, referred to as the phenyl-pyrazolyl-benzotriazoles, wherein the compound has the formula



Ic

Other embodiments of the present invention include those compounds of formula I(c) in combination with each of the aforementioned embodiments of R^2.

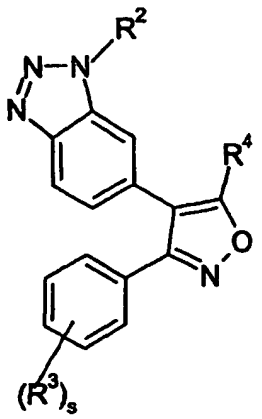
[0047] Another embodiment of the present invention includes compounds of formula I, referred to as the phenyl-oxazolyl-benzotriazoles, wherein the compound has the formula



Id

[0048] Other embodiments of the present invention include those compounds of formula I(d) in combination with each of the aforementioned embodiments of R^2.

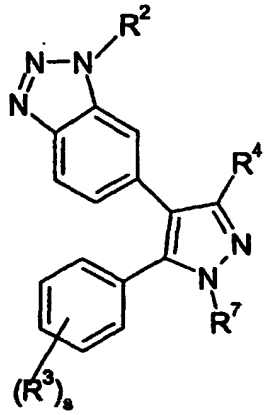
[0049] Another embodiment of the present invention includes compounds of formula I, referred to as the phenyl-isoxazolyl-benzotriazoles, wherein the compound has the formula



Ie

Other embodiments of the present invention include those compounds of formula I(e) in combination with each of the aforementioned embodiments of R^2.

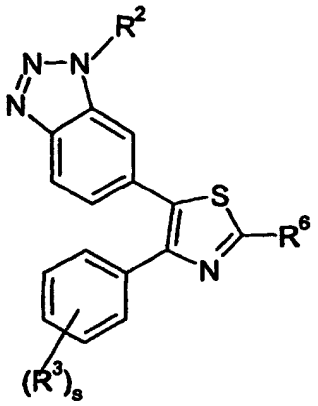
[0050] Another embodiment of the present invention, referred to as the phenyl-pyrazolyl-benzotriazoles, are those group of compounds of formula I wherein the compound has the formula



(f)

Other embodiments of the present invention include those compounds of formula I(f) in combination with each of the aforementioned embodiments of R^2.

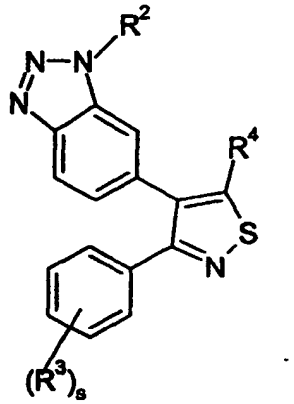
[0051] Another embodiment of the present invention, referred to as the phenyl-thiazolyl-benzotriazoles, are those group of compounds of formula I wherein the compound has the formula



(g)

Other embodiments of the present invention include those compounds of formula I(g) in combination with each of the aforementioned embodiments of R^2.

[0052] Another embodiment of the present invention, referred to as the phenyl-isothiazolyl-benzotriazoles, are those group of compounds of formula I wherein the compound has the formula



(h)

;

Other embodiments of the present invention include those compounds of formula I(h) in combination with each of the aforementioned embodiments of R^2.

[0053] Another preferred embodiment of the present invention is that group of compounds of formula I (and I(a), I (c), I(e), I(f), and I(h)) wherein R^4 is hydrogen. Other embodiments of the present invention include those compounds of formula I (and I(a), I(c), I(e), I(f), and I(h)) wherein R^4 is hydrogen in combination with the aforementioned embodiments of R^2.

[0054] Another embodiment of the present invention is that group of compounds of formula I (and I(a), I(c), I(e), I(f), and I(h)) wherein R^4 is R^9-B-$(CH_2)_n$- and n is zero. Other embodiments of the present invention include those compounds of formula I (and I(a), I(c), I(e), I(f), and I(h)) wherein R^4 is R^9-B-$(CH_2)_n$- and n is zero in combination with the aforementioned embodiments of R^2.

[0055] Another embodiment of the present invention is that group of compounds of formula I (and I(a), I(c), I(e), I(f), and I(h)) wherein R^4 is R^9-B-$(CH_2)_n$- and n is an integer from one to six, more preferably one to five. Other embodiments of the present invention include those compounds of formula I (and I(a), I(c), I(e), I(f), and I(h)) wherein R^4 is R^9-B-$(CH_2)_n$- and n is one to six, preferably one to five, in combination with the aforementioned embodiments of R^2.

[0056] Another preferred embodiment of the present invention is that group of compounds of formula I (and I(a), I (c), I(e), I(f), and I(h)) wherein R^4 is R^9B-$(CH_2)_n$-; n is zero; B is a bond and R^9 is R^{13}-$(R^{12}CH)_m$-. Other embodiments of the present invention include those compounds of formula I (and I(a), I(c), I(e), I(f), and I(h)) wherein R^4 is R^9-B-$(CH_2)_n$-, n is zero and R^9 is R^{13}-$(R^{12}CH)_m$- in combination with the aforementioned embodiments of R^2. Mor preferred embodiments of the invention of formula I (and I(c), I(e) and I(f)) are those compounds wherein R^4 is R^9-B-$(CH_2)_n$-, n is zero, R^9 is R^{13}-$(R^{12}CH)_m$-, m is one to six and R^{12} and R^{13} are each hydrogen.

[0057] Another embodiment of the present invention is that group of compounds of formula I (and I(a), I(c), I(e), I(f), and I(h)) wherein R^4 is R^9-B-$(CH_2)_n$-; n is zero; B is -(C=O)-(R^{10}-N)-, -(R^{10}-N)-, -SO_2-(R^{10}-N)-, -(R^{10}-N)-(C=O)-(NR^{11})- or -(R^{10}-N)-(C=O)-O-; and R^9 is s lected from the group consisting of hydrogen and R^{13}-($R^{12}CH)_m$-; more preferably wherein R^9 is R^{13}-($R^{12}CH)_m$-; m is 1 to 6; R^{10} is hydrogen or methyl; each R^{12} is independently selected from the groups consisting of hydrogen or methyl; and R^{13} is selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic, (C_3-C_{10})cycloalkyl, hydroxy, (C_1-C_6)alkoxy, perhalo (C_1-C_6)alkoxy, phenoxy, (C_1-C_{10})heteroaryl-O-, (C_1-C_{10})heterocyclic-O-, (C_3-C_{10})cycloalkyl-O-, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-NH-SO_2-, -NO_2, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, (C_1-C_6) alkyl-SO_2-NH-, (C_1-C_6)alkyl-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-NH-, phenyl-(C=O) -[((C_1-C_6)alkyl)-N]-, (C_1-C_6)alkyl-SO_2-NH-, phenyl-SO_2-NH-, (C_1-C_6)alkyl-SO_2-[((C_1-C_6)alkyl)-N]-, phenyl-SO_2-[((C_1-C_6)alkyl)-N]-, -CN, (C_1-C_6)alkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6) alkyl]$_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_1-C_6)alkyl-(C=O)-O- and phenyl-(C=O)-O-. Other embodiments of the present invention include those compounds of formula I (and I(a), I(c), I(e), I(f), and I(h)) wherein R^4 is R^9-B-$(CH_2)_n$-; n is zero; B is -(C=O)-(R^{10}-N)-, -(R^{10}-N)-, -SO_2-(R^{10}-N)-, -(R^{10}-N)-(C=O)-(NR^{11})- or -(R^{10}-N)-(C=O)-O-; R^9 is hydrogen or R^{13}-($R^{12}CH)_m$-; more preferably wherein R^9 is R^{13}-($R^{12}CH$)-$_m$; m is 1 to 6; R^{10} is hydrogen or methyl; each R^{12} is independently selected from the groups consisting of hydrogen or methyl; and R^{13} is as described above, in combination with the aforementioned embodiments of R^2.

[0058] Another more preferred embodiment of the present invention is that group of compounds of formula I (and I (a), I(c), I(e), I(f), and I(h)) wherein R^4 is R^9-B-$(CH_2)_n$-; n is zero; B is -(R^{10}-N)-; R^9 is hydrogen or R^{13}-($R^{12}CH)_m$-; m is 1 to 6; R^{10} is hydrogen or methyl; R^{12} is hydrogen or methyl; and R^{13} is selected from the group consisting of hydrogen, (C_1-C_6)alkyl, hydroxy, (C_1-C_6)alkoxy, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$amino, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic and (C_3-C_{10})cycloalkyl. Other embodiments of the present invention include those compounds of formula I (and I(a), I(c), I(e), I(f), and I(h)) wherein R^4 is R^9-B-$(CH_2)_n$-; n is zero; B is -(R^{10}-N)-; R^9 is hydrogen or R^{13}-($R^{12}CH)_m$-; m is 1 to -6; R^{10} is hydrogen or methyl; R^{12} is hydrogen or methyl; and R^{13} is selected from the group consisting of hydrogen, (C_1-C_6)alkyl, hydroxy, (C_1-C_6)alkoxy, amino, (C_1-C_6) alkylamino, [(C_1-C_6)alkyl]$_2$amino, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic and (C_3-C_{10})cycloalkyl, in combination with the aforementioned embodiments of R^1 and R^2. More preferred embodiments of the invention is that group of compounds of formula I (and I(c), I(e) and I(f)) wherein R^4 is R^9-B-$(CH_2)_n$-, n is zero, B is -(R^{10}-N)-, R^9 is R^{13}-($R^{12}CH)_m$-, m is 1 to 6, and R^{10}, R^{12} and R^{13} are each hydrogen.

[0059] Another embodiment of the present invention is that group of compounds of formula I (and I(a), I(c), I(e), I(f), and I(h)) wherein R^4 is R^9-B-$(CH_2)_n$-; n is zero; B is a bond, and R^9 is selected from the group consisting of optionally substituted phenyl, (C_1-C_{10})heterocyclic, (C_1-C_{10})heteroaryl and (C_3-C_{10})cycloalkyl; wherein each of the aforesaid R^9 phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic and (C_3-C_{10})cycloalkyl substituents may optionally be substituted by one to four moieties independently selected from the group consisting of halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6) alkynyl, perhalo(C_1-C_6)alkyl, phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic, (C_3-C_{10})cycloalkyl, hydroxy, (C_1-C_6) alkoxy, perhalo(C_1-C_6)alkoxy, phenoxy, (C_1-C_{10})heteroaryl-O-, (C_1-C_{10})heterocyclic-O-, (C_3-C_{10})cycloalkyl-O-, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-NH-SO_2-, -NO_2, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, (C_1-C_6)alkyl-SO_2-NH-, (C_1-C_6)alkyl-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[((C_1-C_6)alkyl)-N]-, -CN, (C_1-C_6)alkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N(C=O)- (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, (C_1-C_6)alkyl-(C=O)-O- and phenyl-(C=O)-O-. Other embodiments of the present invention include those compounds of formula I (and I(a), I(c), I(e), I(f), and I(h)) wherein wherein R^4 is R^9-B-$(CH_2)_n$-; n is zero; B is a bond, and R^9 is as described above, in combination with the aforementioned embodiments of R^2.

[0060] Another embodiment of the present invention is that group of compounds of formula I (and I(a), I(c), I(e), I(f), and I(h)) wherein R^4 is R^9-B-$(CH_2)_n$-; n is zero; B is -(C=O)-(R^{10}-N)-, -(R^{10}-N)-, -SO_2-(R^{10}-N)-, -(R^{10}-N)-(C=O)-(NR^{11})- or -(R^{10}-N)-(C=O)-O-; and R^9 is selected from the group consisting of optionally substituted phenyl, (C_1-C_{10})heterocyclic, (C_1-C_{10})heteroaryl and (C_3-C_{10})cycloalkyl; wherein each of the aforesaid R^9 phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic and (C_3-C_{10})cycloalkyl substituents may optionally be substituted by one to four moieties independently selected from the group consisting of halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic, (C_3-C_{10})cycloalkyl, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, phenoxy, (C_1-C_{10})heteroaryl-O-, (C_1-C_{10})heterocyclic-O-, (C_3-C_{10})cycloalkyl-O-, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-NH-SO_2-, -NO_2, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, (C_1-C_6)alkyl-SO_2-NH-, (C_1-C_6)alkyl-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[((C_1-C_6)alkyl)-N]-, -CN, (C_1-C_6)alkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cy-

cloalkyl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N(C=O)- (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, (C_1-C_6)alkyl-(C=O)-O- and phenyl-(C=O)-O-. Other embodiments of the present invention include those compounds of formula I (and I(a), I(c), I(e), I(f), and I(h)) wherein R^4 is R^9-B-(CH_2)$_n$-; n is zero; B is -(C=O)-(R^{10}-N)-, -(R^{10}-N)-, -SO_2-(R^{10}-N)-, -(R^{10}-N)-(C=O)-(NR^{11})- or -(R^{10}-N)-(C=O)-O-; and R^9 is as described above, in combination with the aforementioned embodiments of R^2.

[0061] Another embodiment of the present invention is that group of compounds of formula I (and I(a), I(c), I(e), I(f), and I(h)) wherein R^4 is R^9-B-(CH_2)$_n$-; n is an integer from one to six, more preferably one to five, more preferably one to three; B is a bond, and R^9 is selected from the group consisting of optionally substituted phenyl, (C_1-C_{10})heterocyclic, (C_1-C_{10})heteroaryl and (C_3-C_{10})cycloalkyl; wherein each of the aforesaid R^9 phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic and (C_3-C_{10})cycloalkyl substituents may optionally be substituted by one to four moieties independently selected from the group consisting of halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic, (C_3-C_{10})cycloalkyl, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, phenoxy, (C_1-C_{10})heteroaryl-O-, (C_1-C_{10})heterocyclic-O-, (C_3-C_{10})cycloalkyl-O-, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-NH-SO_2-, -NO_2, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, (C_1-C_6)alkyl-SO_2-NH-, (C_1-C_6)alkyl-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[((C_1-C_6)alkyl)-N]-, -CN, (C_1-C_6)alkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N(C=O)- (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, (C_1-C_6)alkyl-(C=O)-O- and phenyl-(C=O)-O-. Other embodiments of the present invention include those compounds of formula I (and I(a), I(c), I(e), I(f), and I(h)) wherein R^4 is R^9-B-(CH_2)$_n$-; n is an integer from one to six, more preferably one to five, more preferably one to three; B is a bond, and R^9 is as described above, in combination with the aforementioned embodiments of R^2.

[0062] Another embodiment of the present invention is that group of compounds of formula I (and I(a), I(c), I(e), I(f), and I(h)) wherein R^4 is R^9-B-(CH_2)$_n$-; n is an integer from one to six, more preferably one to five, more preferably one to three; B is -(C=O)-(R^{10}-N)-, -(R^{10}-N)-, -SO_2-(R^{10}-N)-, -(R^{10}-N)-(C=O)-(NR^{11})- or -(R^{10}-N)-(C=O)-O-; and R^9 is selected from the group consisting of optionally substituted phenyl, (C_1-C_{10})heterocyclic, (C_1-C_{10})heteroaryl and (C_3-C_{10})cycloalkyl; wherein each of the aforesaid R^9 phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic and (C_3-C_{10})cycloalkyl substituents may optionally be substituted by one to four moieties independently selected from the group consisting of halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic, (C_3-C_{10})cycloalkyl, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, phenoxy, (C_1-C_{10})heteroaryl-O-, (C_1-C_{10})heterocyclic-O-, (C_3-C_{10})cycloalkyl-O-, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-NH-SO_2-, -NO_2, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, (C_1-C_6)alkyl-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[((C_1-C_6)alkyl)-N]-, -CN, (C_1-C_6)alkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N(C=O)- (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, (C_1-C_6)alkyl-(C=O)-O- and phenyl-(C=O)-O-. Other embodiments of the present invention include those compounds of formula I (and I(a), I(c), I(e), I(f), and I(h)) wherein R^4 is R^9-B-(CH_2)$_n$-; n is an integer from one to six, more preferably one to five, more preferably one to three; B is -(C=O)-(R^{10}-N)-, -(R^{10}-N)-, -SO_2-(R^{10}-N)-, -(R^{10}-N)-(C=O)-(NR^{11})- or -(R^{10}-N)-(C=O)-O-; and R^9 is as described above, in combination with the aforementioned embodiments of R^2.

[0063] Another embodiment of the present invention is that group of compounds of formula I (and I(a), I(c), I(e), I(f), and I(h)) wherein R^4 is R^9-B-(CH_2)$_n$-; n is an integer from one to six, more preferably one to five, more preferably one to three; B is a bond, and R^9 is R^{13}-(R^{12}CH)$_m$-; m is 1 to 6; R^{10} is hydrogen or methyl; each R^{12} is independently selected from the groups consisting of hydrogen or methyl; and R^{13} is selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic, (C_3-C_{10})cycloalkyl, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, phenoxy, (C_1-C_{10})heteroaryl-O-, (C_1-C_{10})heterocyclic-O-, (C_3-C_{10})cycloalkyl-O-, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-NH-SO_2-, -NO_2, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, (C_1-C_6)alkyl-SO_2-NH-, (C_1-C_6)alkyl-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[((C_1-C_6)alkyl)-N]-, (C_1-C_6)alkyl-SO_2-NH-, phenyl-SO_2-NH-, (C_1-C_6)alkyl-SO_2-[((C_1-C_6)alkyl)-N]-, phenyl-SO_2-[((C_1-C_6)alkyl)-N]-, -CN, (C_1-C_6)alkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_1-C_6)alkyl-(C=O)-O- and phenyl-(C=O)-O-. Other embodiments of the present invention include those compounds of formula I (and I(a), I(c), I(e), I(f), and I(h)) wherein R^4 is R^9-B-(CH_2)$_n$-; n is an integer from one to six, more preferably one to five, more preferably on to thr e; B is a bond, and R^9 is R^{13}-(R^{12}CH)$_m$-; m is 1 to 6; R^{10} is hydrogen or methyl; each R^{12} is independently selected from the groups consisting of hydrogen or methyl; and R^{13} as described above, in combination with the afor m ntioned em-

bodiments of R^2.

[0064] Another embodiment of the present invention is that group of compounds of formula I (and I(a), I(c), I(e), I(f), and I(h)) wherein R^4 is R^9-B-$(CH_2)_n$-; n is an integer from one to six, more preferably one to five, more preferably one to three; B is -(C=O)-(R^{10}-N)-, -(R^{10}-N)-, -SO_2-(R^{10}-N)-, -(R^{10}-N)-(C=O)-(NR^{11})- or -(R^{10}-N)-(C=O)-O-; and R^9 is R^{13}-($R^{12}CH)_m$-; m is 1 to 6; R^{10} is hydrogen or methyl; each R^{12} is independently selected from the groups consisting of hydrogen or methyl; and R^{13} is selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic, (C_3-C_{10})cycloalkyl, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, phenoxy, (C_1-C_{10})heteroaryl-O-, (C_1-C_{10})heterocyclic-O-, (C_3-C_{10})cycloalkyl-O-, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-NH-SO_2-, -NO_2, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, (C_1-C_6)alkyl-SO_2-NH-, (C_1-C_6)alkyl-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[((C_1-C_6)alkyl)-N]-, (C_1-C_6)alkyl-SO_2-NH-, phenyl-SO_2-NH-, (C_1-C_6)alkyl-SO_2-[((C_1-C_6)alkyl)-N]-, phenyl-SO_2-[((C_1-C_6)alkyl)-N]-, -CN, (C_1-C_6)alkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_1-C_6)alkyl-(C=O)-O- and phenyl-(C=O)-O-. Other embodiments of the present invention include those compounds of formula I (and I(a), I(c), I(e), I(f), and I(h)) wherein R^4 is R^9-B-$(CH_2)_n$-; n is an integer from one to six, more preferably one to five, more preferably one to three; B is -(C=O)-(R^{10}-N)-, -(R^{10}-N)-, -SO_2-(R^{10}-N)-, -(R^{10}-N)-(C=O)-(NR^{11})- or -(R^{10}-N)-(C=O)-O-; and R^9 is R^{13}-($R^{12}CH)_m$-; m is 1 to -6; R^{10} is hydrogen or methyl; each R^{12} is independently selected from the groups consisting of hydrogen or methyl; and R^{13} is as described above, in combination with the aforementioned embodiments of R^2.

[0065] Another embodiment of the present invention is that group of compounds of formula I (and I(c) and I(f)) wherein R^7 is selected from the group consisting of hydrogen, phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic, (C_3-C_{10})cycloalkyl, R^{16}-(C_1-C_6)alkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, phenyl-NH-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)- and (C_3-C_{10})cycloalkyl-NH-(C=O)-; wherein each of the aforesaid phenyl, heterocyclic, heteroaryl or cycloalkyl R^7 alternatives may optionally be independently substituted by one to four moieties independently selected from the group consisting of halo, R^{16}-(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, phenyl, benzyl, (C_1-C_{10})heterocyclic, (C_1-C_{10})heteroaryl, (C_1-C_6)alkyl-SO_2-, formyl, -CN, (C_1-C_6)alkyl-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, (C_3-C_{10})cycloalkyl-O-(C=O)-, (C_1-C_{10})heterocyclic-O-(C=O)-, (C_1-C_{10})heteroaryl-O-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, phenyl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, (C_3-C_{10})cycloalkyl-O-, phenoxy, (C_1-C_{10})heterocyclic-O-, (C_1-C_{10})heteroaryl-O-, (C_1-C_6)alkyl-(C=O)-O-, (C_3-C_{10})cycloalkyl-(C=O)-O-, phenyl-(C=O)-O-, (C_1-C_{10})heterocyclic-(C=O)-O-, (C_1-C_{10})heteroaryl-(C=O)-O-, -NO_2, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, formamidyl, (C_1-C_6)alkyl-(C=O)-NH-, (C_3-C_{10})cycloalkyl-(C=O)-NH-, phenyl-(C=O)-NH-, (C_1-C_{10})heterocyclic-(C=O)-NH-, (C_1-C_{10})heteroaryl-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-[((C_1-C_6)alkyl)-N]-, (C_1-C_6)alkyl-SO_2NH-, (C_3-C_{10})cycloalkyl-SO_2NH-, phenyl-SO_2NH-, (C_1-C_{10})heterocyclic-SO_2NH- and (C_1-C_{10})heteroaryl-SO_2NH-; wherein each of said phenyl and heteroaryl moieties may optionally be substituted by one or two radicals independently selected from the group consisting of halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, amino, (C_1-C_6)alkylamino and [(C_1-C_6)alkyl]$_2$-amino. Other embodiments of the present invention include those compounds of formula I (and I(c) and I(f)) wherein R^7 is as defined above, in combination with each of the aforementioned I(c) and I(f) R^4 embodiments and with each of the aforementioned R^2 embodiments.

[0066] Another embodiment of the present invention is that group of compounds of formula I (and I(c) and I(f)) wherein R^7 is selected from the group consisting of R^{16}-(C_1-C_6)alkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, phenyl-NH-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)- and (C_3-C_{10})cycloalkyl-NH-(C=O)-; wherein each of the aforesaid phenyl, heterocyclic, heteroaryl or cycloalkyl R^7 alternatives may optionally be independently substituted by one to four moieties independently selected from the group consisting of halo, R^{16}-(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, phenyl, benzyl, (C_1-C_{10})heterocyclic, (C_1-C_{10})heteroaryl, (C_1-C_6)alkyl-SO_2-, formyl, -CN, (C_1-C_6)alkyl-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, (C_3-C_{10})cycloalkyl-O-(C=O)-, (C_1-C_{10})heterocyclic-O-(C=O)-, (C_1-C_{10})heteroaryl-O-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, phenyl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, (C_3-C_{10})cycloalkyl-O-, phenoxy, (C_1-C_{10})heterocyclic-O-, (C_1-C_{10})heteroaryl-O-, (C_1-C_6)alkyl-(C=O)-O-, (C_3-C_{10})cycloalkyl-(C=O)-O-, phenyl-(C=O)-O-, (C_1-C_{10})heterocyclic-(C=O)-O-, (C_1-C_{10})heteroaryl-(C=O)-O-, -NO_2, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, formamidyl, (C_1-C_6)alkyl-(C=O)-NH-, (C_3-C_{10})cycloalkyl-(C=O)-NH-,

phenyl-(C=O)-NH-, (C_1-C_{10})heterocyclic-(C=O)-NH-, (C_1-C_{10})heteroaryl-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-[((C_1-C_6)alkyl)-N]-, (C_1-C_6)alkyl-SO_2NH-, (C_3-C_{10})cycloalkyl-SO_2NH-, phenyl-SO_2NH-, (C_1-C_{10})heterocyclic-SO_2NH- and (C_1-C_{10})heteroaryl-SO_2NH-; wherein each of said phenyl and heteroaryl moiety alternatives may optionally be substituted by on or two radicals independently selected from the group consisting of halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, amino, (C_1-C_6)alkylamino and [(C_1-C_6)alkyl]$_2$-amino. Other embodiments of the present invention include those compounds of formula I (and I(c) and I(f)) wherein R^7 is as defined above, in combination with each of the aforementioned I(c) and I(f) R^4 embodiments and with each of the aforementioned R^2 embodiments.

[0067] Another preferred embodiment of the present invention is that group of compounds of formula I (and I(c) and I(f)) wherein R^7 is selected from the group consisting of hydrogen, and optionally substituted phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic and (C_3-C_{10})cycloalkyl. Other embodiments of the present invention include those compounds of formula I (and I(c) and I(f)) wherein R^7 is as defined above, in combination with each of the aforementioned I(c) and I(f) R^4 embodiments and with each of the aforementioned R^2 embodiments. A more preferred embodiment of the present invention is that group of compounds of formula I(c) wherein R^7 is hydrogen.

[0068] Another embodiment of the present invention is that group of compounds of formula I (and I(c) and I(f)) wherein R^7 is R^{14}-($CR^{15}H$)$_p$-; p is one to six, preferably one to four; and R^{14} is selected from the group consisting of hydrogen, halo, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, phenyl, (C_1-C_{10})heterocyclic, (C_1-C_{10})heteroaryl, formyl, -CN, (C_1-C_6)alkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, HO-(C=O)-, R^{16}-(C_1-C_6)alkyl-O-(C=O)-, (C_3-C_{10})cycloalkyl-O-(C=O)-, (C_1-C_{10})heterocyclic-O-(C=O)-, (C_1-C_{10})heteroaryl-O-(C=O)-, H_2N-(C=O)-, R^{16}-(C_1-C_6)alkyl-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, phenyl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_1-C_{10})heteroaryl-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_1-C_{10})heterocyclic-[((C_1-C_6)alkyl)-N]-(C=O), (C_3-C_{10})cycloalkyl-[((C_1-C_6)alkyl)-N]-(C=O)-, hydroxy, R^{16}-(C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, (C_3-C_{10})cycloalkyl-O-, phenoxy, (C_1-C_{10})heterocyclic-O-, (C_1-C_{10})heteroaryl-O-, R^{16}-(C_1-C_6)alkyl-(C=O)-O-, (C_3-C_{10})cycloalkyl-(C=O)-O-, phenyl-(C=O)-O-, (C_1-C_{10})heterocyclic-(C=O)-O-, (C_1-C_{10})heteroaryl-(C=O)-O-, amino, R^{16}-(C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, formamidyl, R^{16}-(C_1-C_6)alkyl-(C=O)-NH-, (C_3-C_{10})cycloalkyl-SO_2NH-, phenyl-SO_2NH-, (C_1-C_{10})heterocyclic-SO_2NH- and (C_1-C_{10})heteroaryl-SO_2NH-; wherein each of the aforesaid phenyl, heterocyclic, heteroaryl or cycloalkyl R^{14} alternatives may optionally be independently substituted by one to four moieties independently selected from the group consisting of halo, R^{16}-(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, phenyl, benzyl, (C_1-C_{10})heterocyclic, (C_1-C_{10})heteroaryl, (C_1-C_6)alkyl-SO_2-, formyl, -CN, R^{16}-(C_1-C_6)alkyl-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, (C_3-C_{10})cycloalkyl-O-(C=O)-, (C_1-C_{10})heterocyclic-O-(C=O)-, (C_1-C_{10})heteroaryl-O-(C=O)-, H_2N-(C=O)-, R^{16}-(C_1-C_6)alkyl-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, phenyl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, hydroxy, R^{16}-(C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, (C_3-C_{10})cycloalkyl-O-, phenoxy, (C_1-C_{10})heterocyclic-O-, (C_1-C_{10})heteroaryl-O-, R^{16}-(C_1-C_6)alkyl-(C=O)-O-, (C_3-C_{10})cycloalkyl-(C=O)-O-, phenyl-(C=O)-O-, (C_1-C_{10})heterocyclic-(C=O)-O-, (C_1-C_{10})heteroaryl-(C=O)-O-, -NO_2, amino, R^{16}-(C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, formamidyl, R^{16}-(C_1-C_6)alkyl-(C=O)-NH-, (C_3-C_{10})cycloalkyl-(C=O)-NH-, phenyl-(C=O)-NH-, (C_1-C_{10})heterocyclic-(C=O)-NH-, (C_1-C_{10})heteroaryl-(C=O)-NH-, R^{16}-(C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-[((C_1-C_6)alkyl)-N]-, R^{16}-(C_1-C_6)alkyl-SO_2NH-, (C_3-C_{10})cycloalkyl-SO_2NH-, phenyl-SO_2NH-, (C_1-C_{10})heterocyclic-SO_2NH- and (C_1-C_{10})heteroaryl-SO_2NH-; wherein each of said phenyl and heteroaryl moiety alternatives may optionally be substituted by one or two radicals independently selected from the group consisting of halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, amino, (C_1-C_6)alkylamino or [(C_1-C_6)alkyl]$_2$-amino;

each R^{15} is independently selected from the group consisting of hydrogen, halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, perhalo(C_1-C_6)alkyl, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, formamidyl and (C_1-C_6)alkyl-(C=O)-NH-; and

each R^{16} is independently selected from the group consisting of hydrogen, halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, (C_1-C_6)alkyl-(C=O)-O-, -NO_2, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, formamidyl and (C_1-C_6)alkyl-(C=O)-NH-. Other embodiments of the present invention include those compounds of formula I (and I(c) and I(f)) wherein R^7 is as defined above, in combination with each of the aforementioned I(c) and I(f) R^4 embodiments and with each of the aforementioned R^2 embodiments.

[0069] Another preferred embodiment of the present invention is that group of compounds of formula I (and I(c) and I(f)) wh rein R^7 is R^{14}-($CR^{15}H$)$_p$-; p is one to four; R^{14} is selected from the group consisting of hydrogen, halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_3-C_{10})cycloalkyl, phenyl, (C_1-C_{10})heterocyclic, (C_1-C_{10})heteroaryl, HO-(C=O)-, R^{16}-(C_1-C_6)alkyl-O-(C=O)-, H_2N-(C=O)-, R^{16}-(C_1-C_6)alkyl-NH-(C=O)-, phenyl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-,

[(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-[N-((C_1-C_6)alkyl)]-(C=O)-, hydroxy, R^{16}-(C_1-C_6)alkoxy, phenoxy, amino, R^{16}-(C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino and R^{16}-(C_1-C_6)alkyl-(C=O)-NH-; wherein each of the aforesaid phenyl, heterocyclic, heteroaryl or cycloalkyl R^{14} alternatives may optionally be independently substituted by one to four moieties independently selected from the group consisting of halo, R^{16}-(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, (C_1-C_6)alkyl-SO_2-, formyl, -CN, R^{16}-(C_1-C_6)alkyl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N-(C=O)-, R^{16}-(C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, hydroxy, R^{16}-(C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, R^{16}-(C_1-C_6)alkyl-(C=O)-O-, amino, R^{16}-(C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, formamidyl, R^{16}-(C_1-C_6)alkyl-(C=O)-NH-, R^{16}-(C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]- and R^{16}-(C_1-C_6)alkyl-SO_2NH-;

each R^{15} is independently selected from the group consisting of hydrogen, halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, perhalo(C_1-C_6)alkyl, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, formamidyl and (C_1-C_6)alkyl-(C=O)-NH-; wherein no more than two of said R^{15} groups may be other than hydrogen; and

each R^{16} is independently selected from the group consisting of hydrogen, halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, (C_1-C_6)alkyl-(C=O)-O-, -NO_2, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, formamidyl and (C_1-C_6)alkyl-(C=O)-NH-. Other embodiments of the present invention include those compounds of formula I (and I(c) and I(f)) wherein R^7 is as defined above, in combination with each of the aforementioned I(c) and I(f) R^4 embodiments and with each of the aforementioned R^2 embodiments.

[0070] A more preferred embodiment of the present invention are those group of compounds of formula I(c) wherein R^7 is R^{14}-($CR^{15}H$)$_p$-; p is one to four; R^{14} is selected from the group consisting of hydrogen, (C_2-C_4)alkenyl, HO-(C=O)-, (C_1-C_3)alkyl-O-(C=O)-, H_2N-(C=O)-, (C_1-C_3)alkyl-NH-(C=O)-, [(C_1-C_2)alkyl]$_2$-N-(C=O)-, hydroxy, (C_1-C_3)alkoxy, amino, (C_1-C_4)alkylamino, [(C_1-C_4)alkyl]$_2$-amino and (C_1-C_3)alkyl-(C=O)-NH-; and each R^{15} is independently selected from the group consisting of hydrogen, (C_1-C_2)alkyl, hydroxy, and amino. More preferred compounds of formula I(c) are those compounds wherein the combined molecular weight of the R^4 and R^7 substituents is less than 200 AMU. More preferably, the combined molecular weight of the R^4 and R^7 substituents is less than 100 AMU.

[0071] Another embodiment of the present invention is that group of compounds of formula I (and I(b)) wherein R^5 is hydrogen. Other embodiments of the present invention include those compounds of formula I (and.I(b)) wherein R^5 is hydrogen, in combination with each of the aforementioned R^2 embodiments.

[0072] Another preferred embodiment of the present invention is that group of compounds of formula I (and I(b)) wherein R^5 is (C_1-C_{10})heterocyclic or (C_1-C_{10})heteroaryl; wherein each of the aforesaid heterocyclic and heteroaryl substituents may optionally be independently substituted by one to four moieties independently selected from the group consisting of halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)- and [(C_1-C_6)alkyl]$_2$-N-(C=O)-. Other embodiments of the present invention include those compounds of formula I (and I(b)) wherein R^5 is said optionally substituted (C_1-C_{10})heterocyclic or (C_1-C_{10})heteroaryl, in combination with each of the aforementioned R^2 embodiments. More preferred heterocyclic groups are pyrrolidinyl, piperidinyl and azetidinyl.

[0073] Another preferred embodiment of the present invention is that group of compounds of formula I (and I(b)) wherein R^5 is R^{14}-(CHR^{15})$_p$-, p is 1 to 6; and R^{14} is selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, perhalo(C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, phenyl, (C_1-C_{10})heterocyclic, (C_1-C_{10})heteroaryl, phenyl-(S=O)-, (C_1-C_6)alkyl-SO_2, phenyl-SO_2-, H_2N-SO_2-, (C_1-C_6)alkyl-NH-SO_2-, phenyl-NH-SO_2-, [(C_1-C_6)alkyl-]$_2$N-SO_2-, (C_1-C_6)alkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, (C_3-C_{10})cycloalkyl-O-(C=O)-, (C_1-C_{10})heterocyclic-O-(C=O)-, (C_1-C_{10})heteroaryl-O-(C=O)-, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, phenyl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_1-C_{10})heteroaryl-[N-(C_1-C_6)alkyl]-(C=O)-, (C_1-C_{10})heterocyclic-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_3-C_{10})cycloalkyl[((C_1-C_6)alkyl)-N]-(C=O)-, hydroxy, R^{16}-(C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, (C_3-C_{10})cycloalkyl-O-, phenoxy, (C_1-C_{10})heterocyclic-O-, (C_1-C_{10})heteroaryl-O-, R^{16}-(C_1-C_6)alkyl-(C=O)-O-, (C_3-C_{10})cycloalkyl-(C=O)-O-, phenyl-(C=O)-O-, (C_1-C_{10})heterocyclic-(C=O)-O-, (C_1-C_{10})heteroaryl-(C=O)-O-, -NO_2, amino, R^{16}-(C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, formamidyl, R^{16}-(C_1-C_6)alkyl-(C=O)-NH-, (C_3-C_{10})cycloalkyl-(C=O)-NH-, phenyl-(C=O)-NH-, R^{16}-(C_1-C_6)alkyl-SO_2NH-, (C_3-C_{10})cycloalkyl-SO_2NH-, phenyl-SO_2NH-, (C_1-C_{10})heterocyclic-SO_2NH- and (C_1-C_{10})heteroaryl-SO_2NH-; wherein each of the aforesaid phenyl, heterocyclic, heteroaryl or cycloalkyl R^{14} alternatives may optionally be independently substituted by one to four moieties independently selected from the group consisting of halo, R^{16}-(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, phenyl, benzyl, (C_1-C_{10})heterocyclic, (C_1-C_{10})heteroaryl, (C_1-C_6)alkyl-SO_2-, formyl, -CN, R^{16}-(C_1-C_6)alkyl-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, (C_3-C_{10})cycloalkyl-O-(C=O)-, (C_1-C_{10})heterocyclic-O-(C=O)-, (C_1-C_{10})heteroaryl-O-(C=O)-, H_2N-(C=O)-, R^{16}-(C_1-C_6)alkyl-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, phenyl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, hy-

droxy, R^{16}-(C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, (C_3-C_{10})cycloalkyl-O-, phenoxy, (C_1-C_{10})heterocyclic-O-, (C_1-C_{10})heteroaryl-O-, R^{16}-(C_1-C_6)alkyl-(C=O)-O-, (C_3-C_{10})cycloalkyl-(C=O)-O-, phenyl-(C=O)-O-, (C_1-C_{10})heterocyclic-(C=O)-O-, (C_1-C_{10})heteroaryl-(C=O)-O-, $-NO_2$, amino, R^{16}-(C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, formamidyl, R^{16}-(C_1-C_6)alkyl-(C=O)-NH-, (C_3-C_{10})cycloalkyl-(C=O)-NH-, phenyl-(C=O)-NH-, (C_1-C_{10})heterocyclic-(C=O)-NH-, (C_1-C_{10})heteroaryl-(C=O)-NH-, R^{16}-(C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-[(C_1-C_6)alkyl-N]-, R^{16}-(C_1-C_6)alkyl-SO_2NH-, (C_3-C_{10})cycloalkyl-SO_2NH-, phenyl-SO_2NH-, (C_1-C_{10})heterocyclic-SO_2NH- and (C_1-C_{10})heteroaryl-SO_2NH-; and wherein each of said phenyl and heteroaryl moiety alternatives may optionally be substituted by one or two radicals independently selected from halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, amino, (C_1-C_6)alkylamino and [(C_1-C_6)alkyl]$_2$-amino. Other embodiments of the present invention include those compounds of formula I (and I(b)) wherein R^5 is said R^{14}-$(CHR^{15})_p$-, p is 1 to -6; and R^{14} is as defined above, in combination with each of the aforementioned R^2 embodiments.

[0074] Another preferred embodiment of the present invention is that group of compounds of formula I (and I(b)) wherein R^5 is R^{14}-$(CHR^{15})_p$-, p is 1 to 6; and R^{14} is selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_3-C_{10})cycloalkyl, phenyl, (C_1-C_{10})heterocyclic, (C_1-C_{10})heteroaryl, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, phenyl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, hydroxy, R^{16}-(C_1-C_6)alkoxy, phenoxy, amino, R^{16}-(C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, R^{16}-(C_1-C_6)alkyl-(C=O)-NH-; wherein each of the aforesaid phenyl, heterocyclic, heteroaryl or cycloalkyl R^{14} substituents may optionally be independently substituted by one to four moieties independently selected from the group consisting of halo, R^{16}-(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, (C_1-C_6)alkyl-SO_2-, formyl, -CN, R^{16}-(C_1-C_6)alkyl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N-(C=O)-, R^{16}-(C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, hydroxy, R^{16}-(C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, R^{16}-(C_1-C_6)alkyl-(C=O)-O-, amino, R^{16}-(C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, formamidyl, R^{16}-(C_1-C_6)alkyl-(C=O)-NH-, R^{16}-(C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]- and R^{16}-(C_1-C_6)alkyl-SO_2NH-;

each R^{15} is independently selected from the group consisting of hydrogen, halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, perhalo(C_1-C_6)alkyl, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, formamidyl and (C_1-C_6)alkyl-(C=O)-NH-; wherein no more than two of said R^{15} groups may be other than hydrogen; and

each R^{16} is independently selected from the group consisting of hydrogen, halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, (C_1-C_6)alkyl-(C=O)-O-, $-NO_2$, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, formamidyl and (C_1-C_6)alkyl-(C=O)-NH-.

[0075] Other embodiments of the present invention include that group of compounds of formula I (and I(b)) wherein R^5 is said R^{14}-$(CHR^{15})_p$-, p is 1 to 6; and R^{14}, R^{15} and R^{16} are as defined above, in combination with each of the aforementioned R^2 embodiments.

[0076] A more preferred embodiment of the present invention are those group of compounds of formula I (and I(b)) wherein R^5 is R^{14}-$(CHR^{15})_p$-, p is 1 to 6; and R^{14} is selected from the group consisting of hydrogen, (C_2-C_4)alkenyl, (C_1-C_{10})heterocyclic, HO-(C=O)-, (C_1-C_3)alkyl-O-(C=O)-, H_2N-(C=O)-, (C_1-C_3)alkyl-NH-(C=O)-, hydroxy, (C_1-C_3)alkoxy, amino, (C_1-C_3)alkylamino, and [(C_1-C_2)alkyl]$_2$-amino; and each R^{15} is independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, hydroxy, (C_1-C_3)alkoxy, perhalo(C_1)alkoxy, amino, (C_1-C_2)alkylamino, [(C_1-C_2)alkyl]$_2$-amino, formamidyl and (C_1-C_6)alkyl-(C=O)-NH-; wherein no more than two of said R^{15} groups may be other than hydrogen.

[0077] Another embodiment of the present invention is that group of compounds of formula I (and I(a), I(b), I(d), I(g)) wherein R^6 is hydrogen. Other embodiments of the present invention include those compounds of formula I (and I(a), I(b), I(d), I(g)) wherein R^6 is hydrogen, in combination with each of the aforementioned I(a) R^4 embodiments, I(b) R^5 embodiments or with each of the aforementioned R^2 embodiments.

[0078] Another embodiment of the present invention is that group of compounds of formula I (and I(a), I(b), I(d), I(g)) wherein R^6 is R^9-B-$(CH_2)_n$- and n is zero. Other embodiments of the present invention include those compounds of formula I (and I(a), I(b), I(d), I(g)) wherein R^6 is R^9-B-$(CH_2)_n$- and n is zero, in combination with each of the aforementioned I(a) R^4 embodiments, I(b) R^5 embodiments or with each of the aforementioned R^2 embodiments.

[0079] Another embodiment of the present invention is that group of compounds of formula I (and I(a), I(b), I(d), I(g)) wherein R^6 is R^9-B-$(CH_2)_n$- and n is an integer from one to six, more preferably from one to five. Other embodiments of the present invention include those compounds of formula I (and I(a), I(b), I(d), I(g)) wherein R^6 is R^9-B-$(CH_2)_n$- and n is an integer from one to six, more preferably from one to five, in combination with each of the aforementioned I(a) R^4 embodiments, I(b) R^5 embodiments or with each of the aforementioned R^2 embodiments.

[0080] Another preferred embodiment of the present invention is that group of compounds of formula I (and I(a), I(b), I(d), I(g)) wherein R^6 is R^9B-$(CH_2)_n$-; n is zero; B is a bond and R^9 is selected from the group consisting of hydrogen, $-CF_3$, -C≡N, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic or (C_3-C_{10})cycloalkyl; wherein each of the aforesaid (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic and (C_3-C_{10})cycloalkyl may optionally be substituted by one to three moieties ind -

pendently selected from the group consisting of halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_1-C_6)alkynyl, perhalo(C_1-C_6)alkyl, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-NH-SO_2-, $-NO_2$, amino, (C_1-C_6)alkylamino, $[(C_1-C_6)alkyl]_2$-amino, (C_1-C_6)alkyl-SO_2-NH-, (C_1-C_6)alkyl-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, -CN, (C_1-C_6)alkyl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, $H_2N(C=O)$-, (C_1-C_6)alkyl-NH-(C=O)-, $[(C_1-C_6)alkyl]_2$-N-(C=O)- and (C_1-C_6)alkyl-(C=O)-O-. Other embodiments of the present invention include those compounds of formula I (and I(a), I(b), I(d), I(g)) wherein R^6 is R^9-B-$(CH_2)_n$- and n is zero; B is a bond and R^9 is as defined above, in combination with each of the aforementioned I(a) R^4 embodiments, I(b) R^5 embodiments or with each of the aforementioned R^2 embodiments.

[0081] Another embodiment of the present invention is that group of compounds of formula I (and I(a), I(b), I(d), I (g)) wherein R^6 is R^9-B-$(CH_2)_n$-; n is zero; B is -(C=O)-NR^{10}-, -(R^{10}-N)-, -(R^{10}-N)-SO_2-, -(R^{10}-N)-(C=O)-, >C=O, -O-(C=O)-, -SO_2-(NR^{10})-, -(R^{10}-N)-(C=O)-(NR^{11})-; and

R^9 is selected from the group consisting of hydrogen, (C_3-C_{10})cycloalkyl or phenyl; wherein the aforesaid phenyl and (C_3-C_{10})cycloalkyl may optionally be substituted by one to three moieties independently selected from the group consisting of halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, hydroxy, (C_1-C_6)alkoxy, perhalo (C_1-C_6)alkoxy, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-NH-SO_2-, $-NO_2$, amino, (C_1-C_6)alkylamino, $[(C_1-C_6)alkyl]_2$-amino, (C_1-C_6)alkyl-SO_2-NH-, (C_1-C_6)alkyl-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-[N(C_1-C_6)alkyl]-, -CN, (C_1-C_6)alkyl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, $H_2N(C=O)$- (C_1-C_6)alkyl-NH-(C=O)-, $[(C_1-C_6)alkyl]_2$-N-(C=O)- and (C_1-C_6)alkyl-(C=O)-O-. Other embodiments of the present invention include those compounds of formula I (and I(a), I (b), I(d), I(g)) wherein R^6 is R^9-B-$(CH_2)_n$- and n is zero; B is -(C=O)-NR^{10}-, -(R^{10}-N)-, -(R^{10}-N)-SO_2-, -(R^{10}-N)-(C=O)-, >C=O, -O-(C=O)-, -SO_2-(NR^{10})-, -(R^{10}-N)-(C=O)-(NR^{11})-; and R^9 is as defined above, in combination with each of the aforementioned I(a) R^4 embodiments, I(b) R^5 embodiments or with each of the aforementioned R^2 embodiments.

[0082] Another embodiment of the present invention is that group of compounds of formula I (and I(a), I(b), I(d), I (g)) wherein R^6 is R^9-B-$(CH_2)_n$-; n is zero; B is a bond; R^9 is R^{13}-$(R^{12}CH)_m$-; m is 1 to 6; R^{10} is hydrogen or methyl; R^{12} is hydrogen or methyl; and R^{13} is selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic, (C_3-C_{10})cycloalkyl, amino, (C_1-C_6)alkylamino, $[(C_1-C_6)alkyl]_2$amino, (C_1-C_6)alkyl-SO_2-NH-, phenyl-SO_2-NH-, (C_1-C_6)alkyl-SO_2-[N-(C_1-C_6)alkyl]-, phenyl-SO_2-[N-(C_1-C_6)alkyl]-, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, phenoxy, (C_1-C_{10})heteroaryl-O-, (C_1-C_{10})heterocyclic-O-, (C_3-C_{10})cycloalkyl-O-, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-NH-SO_2-, $-NO_2$, amino, (C_1-C_6)alkylamino, $[(C_1-C_6)alkyl]_2$-amino, (C_1-C_6)alkyl-SO_2-NH-, (C_1-C_6)alkyl-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-[N(C_1-C_6)alkyl]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[N-(C_1-C_6)alkyl]-, -CN, (C_1-C_6)alkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, $H_2N(C=O)$-, (C_1-C_6)alkyl-NH-(C=O)-, $[(C_1-C_6)alkyl]_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[N-((C_1-C_6)alkyl)]-(C=O)-, (C_1-C_6)alkyl-(C=O)-O- and phenyl-(C=O)-O-. Other embodiments of the present invention include those compounds of formula I (and I(a), I(b), I(d), I(g)) wherein R^6 is R^9-B-$(CH_2)_n$- and n is zero; B is a bond; R^9 is R^{13}-$(R^{12}CH)_m$-; m is 1 to 6; R^{10} is hydrogen or methyl; R^{12} is hydrogen or methyl; and R^{13} is as defined above, in combination with each of the aforementioned I(a) R^4 embodiments, I(b) R^5 embodiments or with each of the aforementioned R^2 embodiments.

[0083] Another preferred embodiment of the present invention is that group of compounds of formula I (and I(a), I (b), I(d), I(g)) wherein R^6 is R^9-B-$(CH_2)_n$-; n is zero; B is -(C=O)-NR^{10}-, -(R^{10}-N)-, >C=O, -O-(C=O)-, -(R^{10}-N)-(C=O)- or -(R^{10}-N)-(C=O)-(NR^{11})-; R^9 is R^{13}-$(R^{12}CH)_m$-; m is 1 to 6; R^{10} is hydrogen or methyl; R^{12} is hydrogen or methyl; and R^{13} is selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic, (C_3-C_{10})cycloalkyl, amino, (C_1-C_6)alkylamino, $[(C_1-C_6)alkyl]_2$amino, (C_1-C_6)alkyl-SO_2-NH-, phenyl-SO_2-NH-, (C_1-C_6)alkyl-SO_2-[N-(C_1-C_6)alkyl]-, phenyl-SO_2-[N-(C_1-C_6)alkyl]-, hydroxy, (C_1-C_6)alkoxy, perhalo (C_1-C_6)alkoxy, phenoxy, (C_1-C_{10})heteroaryl-O-, (C_1-C_{10})heterocyclic-O-, (C_3-C_{10})cycloalkyl-O-, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-NH-SO_2-, $-NO_2$, amino, (C_1-C_6)alkylamino, $[(C_1-C_6)alkyl]_2$-amino, (C_1-C_6)alkyl-SO_2-NH-, (C_1-C_6)alkyl-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-[N(C_1-C_6)alkyl]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[N-(C_1-C_6)alkyl]-, -CN, (C_1-C_6)alkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, HO-(C=O)-, (C_1-C_8)alkyl-O-(C=O)-, $H_2N(C=O)$-, (C_1-C_6)alkyl-NH-(C=O)-, $[(C_1-C_6)alkyl]_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[N-((C_1-C_6)alkyl)]-(C=O)-, (C_1-C_6)alkyl-(C=O)-O- and phenyl-(C=O)-O-. Other embodiments of the present invention include those compounds of formula I (and I(a), I(b), I(d), I(g)) wherein R^6 is R^9-B-$(CH_2)_n$- and n is zero; B is -(C=O)-NR^{10}-, -(R^{10}-N)-, -(R^{10}-N)-SO_2-, -(R^{10}-N)-(C=O)-, >C=O, -O-(C=O)-, -SO_2-(NR^{10})-, -(R^{10}-N)-(C=O)-(NR^{11})-; and R^9 is R^{13}-$(R^{12}CH)_m$-; m is 1 to 6; R^{10} is hydrogen or methyl; R^{12} is hydrogen or methyl; and R^{13} is as defined above, in combination with each of the aforementioned I(a) R^4 embodiments, I(b) R^5 embodiments or with each of the aforementioned R^2 embodiments.

[0084] Another embodiment of the present invention is that group of compounds of formula I (and I(a), I(b), I(d), I (g)) wherein R^6 is R^9-B-$(CH_2)_n$-; n is an integer from one to six, more preferably one to five, more preferably one to three; B is a bond, and R^9 is selected from the group consisting of optionally substituted phenyl, (C_1-C_{10})heterocyclic,

(C_1-C_{10})heteroaryl and (C_3-C_{10})cycloalkyl; wherein each of the aforesaid R^9 phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic and (C_3-C_{10})cycloalkyl substituents may optionally be substituted by one to four moieties independently selected from the group consisting of halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic, (C_3-C_{10})cycloalkyl, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, phenoxy, (C_1-C_{10})heteroaryl-O-, (C_1-C_{10})heterocyclic-O-, (C_3-C_{10})cycloalkyl-O-, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-NH-SO_2-, -NO_2, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, (C_1-C_6)alkyl-SO_2-NH-, (C_1-C_6)alkyl-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[((C_1-C_6)alkyl)-N]-, -CN, (C_1-C_6)alkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N(C=O)-(C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, (C_1-C_6)alkyl-(C=O)-O- and phenyl-(C=O)-O-. Other embodiments of the present invention include those compounds of formula I (and I(a), I(b), I(d), I(g))wherein R^6 is R^9-B-(CH_2)$_n$-; n is an integer from one to six, more preferably one to five, more preferably one to three; B is a bond, and R^9 is as described above, in combination with each of the aforementioned I(a) R^4 embodiments, I(b) R^5 embodiments or with each of the aforementioned R^2 embodiments..

[0085] Another embodiment of the present invention is that group of compounds of formula I (and I(a), I(b), I(d), I (g)) wherein R^6 is R^9-B-(CH_2)$_n$-; n is an integer from one to six, more preferably one to five, more preferably one to three; B is -(C=O)-(R^{10}-N)-, -(R^{10}-N)-, -SO_2-(R^{10}-N)-, -(R^{10}-N)-(C=O)-(NR^{11})- or -(R^{10}-N)-(C=O)-O-; and R^9 is selected from the group consisting of optionally substituted phenyl, (C_1-C_{10})heterocyclic, (C_1-C_{10})heteroaryl and (C_3-C_{10})cycloalkyl; wherein each of the aforesaid R^9 phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic and (C_3-C_{10})cycloalkyl substituents may optionally be substituted by one to four moieties independently selected from the group consisting of halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocydic, (C_3-C_{10})cycloalkyl, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, phenoxy, (C_1-C_{10})heteroaryl-O-, (C_1-C_{10})heterocyclic-O-, (C_3-C_{10})cycloalkyl-O-, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-NH-SO_2-, -NO_2, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, (C_1-C_6)alkyl-SO_2-NH-, (C_1-C_6)alkyl-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[((C_1-C_6)alkyl)-N]-, -CN, (C_1-C_6)alkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N(C=O)-(C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, (C_1-C_6)alkyl-(C=O)-O- and phenyl-(C=O)-O-. Other embodiments of the present invention include those compounds of formula I (and I(a), I(b), I(d), I(g)) wherein R^6 is R^9B-(CH_2)$_n$-; n is an integer from one to six, more preferably one to five, more preferably one to three; B is -(C=O)-(R^{10}-N)-, -(R^{10}-N)-, -SO_2-(R^{10}-N)-, -(R^{10}-N)-(C=O)-(NR^{11})- or -(R^{10}-N)-(C=O)-O-; and R^9 is as described above, in combination with each of the aforementioned I(a) R^4 embodiments, I(b) R^5 embodiments or with each of the aforementioned R^2 embodiments.

[0086] Another embodiment of the present invention is that group of compounds of formula I (and I(a), I(b), I(d), I (g)) wherein R^6 is R^9-B-(CH_2)$_n$-; n is an integer from one to six, more preferably one to five, more preferably one to three; B is a bond, and R^9 is R^{13}-($R^{12}CH$)$_m$-; m is 1 to 6; R^{10} is hydrogen or methyl; each R^{12} is independently selected from the groups consisting of hydrogen or methyl; and R^{13} is selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic, (C_3-C_{10})cycloalkyl, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, phenoxy, (C_1-C_{10})heteroaryl-O-, (C_1-C_{10})heterocyclic-O-, (C_3-C_{10})cycloalkyl-O-, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-SO_2-, (C_1-C_6)alkyl-NH-SO_2-, -NO_2, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, (C_1-C_6)alkyl-SO_2-NH-, (C_1-C_6)alkyl-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[((C_1-C_6)alkyl)-N]-, (C_1-C_6)alkyl-SO_2-NH-, phenyl-SO_2-NH-, (C_1-C_6)alkyl-SO_2-[((C_1-C_6)alkyl)-N]-, phenyl-SO_2-[((C_1-C_6)alkyl)-N]-, -CN, (C_1-C_6)alkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_1-C_6)alkyl-(C=O)-O- and phenyl-(C=O)-O-. Other embodiments of the present invention include those compounds of formula I (and I(a), I(c), I(e), I(f), and I(h)) wherein R^6 is R^9-B-(CH_2)$_n$-; n is an integer from one to six, more preferably one to five, more preferably one to three; B is -(C=O)-(R^{10}-N)-, -(R^{10}-N)-, -SO_2-(R^{10}-N)-, -(R^{10}-N)-(C=O)-(NR^{11})- or -(R^{10}-N)-(C=O)-O-; R^9 is R^{13}-($R^{12}CH$)$_m$-; m is 1 to 6; R^{10} is hydrogen or methyl; each R^{12} is independently selected from the groups consisting of hydrogen or methyl; and R^{13} is as described above, in combination with each of the aforementioned I(a) R^4 embodiments, I(b) R^5 embodiments or with each of the aforementioned R^2 embodiments.

[0087] Another preferred embodiment of the present invention is that group of compounds of formula I (and I(a), I (b), I(d), I(g)) wherein R^6 is R^9-B-(CH_2)$_n$-; n is an interger from one to six; B is -(C=O)-NR^{10}-, -(R^{10}-N)-, >C=O, -O-(C=O)-, -(R^{10}-N)-(C=O)- or -(R^{10}-N)-(C=O)-(NR^{11})-; R^9 is R^{13}-($R^{12}CH$)$_m$-; m is 1 to 6; R^{10} is hydrogen or methyl; R^{12} is hydrogen or methyl; and R^{13} is selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic, (C_3-C_{10})cycloalkyl, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$amino,

$(C_1$-$C_6)$alkyl-SO_2-NH-, phenyl-SO_2-NH-, $(C_1$-$C_6)$alkyl-SO_2-[N-$(C_1$-$C_6)$alkyl]-, phenyl-SO_2-[N-$(C_1$-$C_6)$alkyl]-, hydroxy, $(C_1$-$C_6)$alkoxy, perhalo$(C_1$-$C_6)$alkoxy, phenoxy, $(C_1$-$C_{10})$heteroaryl-O-, $(C_1$-$C_{10})$heterocyclic-O-, $(C_3$-$C_{10})$cycloalkyl-O-, $(C_1$-$C_6)$alkyl-S-, $(C_1$-$C_6)$alkyl-SO_2-, $(C_1$-$C_6)$alkyl-NH-SO_2-, -NO_2, amino, $(C_1$-$C_6)$alkylamino, $[(C_1$-$C_6)$alkyl$]_2$-amino, $(C_1$-$C_6)$alkyl-SO_2-NH-, $(C_1$-$C_6)$alkyl-(C=O)-NH-, $(C_1$-$C_6)$alkyl-(C=O)-[N$(C_1$-$C_6)$alkyl]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[N-$(C_1$-$C_6)$alkyl]-, -CN, $(C_1$-$C_6)$alkyl-(C=O)-, phenyl-(C=O)-, $(C_1$-$C_{10})$heteroaryl-(C=O)-, $(C_1$-$C_{10})$heterocyclic-(C=O)-, $(C_3$-$C_{10})$cycloalkyl-(C=O)-, $(C_1$-$C_{10})$heteroaryl-NH-(C=O)-, $(C_1$-$C_{10})$heterocyclic-NH-(C=O)-, $(C_3$-$C_{10})$cycloalkyl-NH-(C=O)-, HO-(C=O)-, $(C_1$-$C_6)$alkyl-O-(C=O)-, H_2N(C=O)-, $(C_1$-$C_6)$alkyl-NH-(C=O)-, $[(C_1$-$C_6)$alkyl$]_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[N-$((C_1$-$C_6)$alkyl)]-(C=O)-, $(C_1$-$C_6)$alkyl-(C=O)-O- and phenyl-(C=O)-O-. Other embodiments of the present invention include those compounds of formula I (and I(a), I(b), I(d), I(g)) wherein R^6 is R^9-B-$(CH_2)_n$- and n is 1 to 6; B is -(C=O)-NR^{10}-, -(R^{10}-N)-, -(R^{10}-N)-SO_2-, -(R^{10}-N)-(C=O)-, >C=O, -O-(C=O)-, -SO_2-(NR^{10})-, -(R^{10}-N)-(C=O)-(NR^{11})-; and R^9 is R^{13}-($R^{12}CH)_m$-; m is 1 to 6; R^{10} is hydrogen or methyl; R^{12} is hydrogen or methyl; and R^{13} is as defined above, in combination with each of the aforementioned I(a) R^4 embodiments, I(b) R^5 embodiments or with each of the aforementioned R^2 embodiments.

[0088] An embodiment of the present invention is that group of compounds of formula I wherein s is an integer from zero to four and each R^3 is independently selected from the group consisting of halo, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, perhalo$(C_1$-$C_6)$alkyl, phenyl, $(C_1$-$C_{10})$heteroaryl, $(C_1$-$C_{10})$heterocyclic, $(C_3$-$C_{10})$cycloalkyl, hydroxy, $(C_1$-$C_6)$alkoxy, perhalo$(C_1$-$C_6)$alkoxy, phenoxy, $(C_1$-$C_{10})$heteroaryl-O-, $(C_1$-$C_{10})$heterocyclic-O-, $(C_3$-$C_{10})$cycloalkyl-O-, $(C_1$-$C_6)$alkyl-S-, $(C_1$-$C_6)$alkyl-SO_2-, $(C_1$-$C_6)$alkyl-NH-SO_2-, -NO_2, amino, $(C_1$-$C_6)$alkylamino, $[(C_1$-$C_6)$alkyl$]_2$-amino, $(C_1$-$C_6)$alkyl-SO_2-NH-, $(C_1$-$C_6)$alkyl-(C=O)-NH-, $(C_1$-$C_6)$alkyl-(C=O)-[$((C_1$-$C_6)$alkyl)-N]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[$((C_1$-$C_6)$alkyl)-N]-, -CN, $(C_1$-$C_6)$alkyl-(C=O)-, phenyl-(C=O)-, $(C_1$-$C_{10})$heteroaryl-(C=O)-, $(C_1$-$C_{10})$heterocyclic-(C=O)-, $(C_3$-$C_{10})$cycloalkyl-(C=O)-, HO-(C=O)-, $(C_1$-$C_6)$alkyl-O-(C=O)-, H_2N(C=O)-, $(C_1$-$C_6)$alkyl-NH-(C=O)-, $[(C_1$-$C_6)$alkyl$]_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[$((C_1$-$C_6)$alkyl)-N]-(C=O)-, $(C_1$-$C_{10})$heteroaryl-NH-(C=O)-, $(C_1$-$C_{10})$heterocyclic-NH-(C=O)-, $(C_3$-$C_{10})$cycloalkyl-NH-(C=O)- and $(C_1$-$C_6)$alkyl-(C=O)-O-. Other embodiments of the present invention include those compounds of formula I (and I(a), I(b), I(c), I(d), I(e), I(f) and I(g)) wherein R^3 is as defined above in combination with each of the aforementioned R^6 embodiments, R^7 embodiments, R^4 embodiments, R^5 embodiments or with each of the aforementioned R^2 embodiments.

[0089] Another embodiment of the present invention is that group of compounds of formula I wherein s is an integer from zero to four and each R^3 is independently selected from the group consisting of halo, -CN, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl and perhalo$(C_1$-$C_6)$alkyl. Other embodiments of the present invention include those compounds of formula I (and I(a), I(b), I(c), I(d), I(e), I(f) and I(g)) wherein R^3 is as defined above in combination with each of the aforementioned R^6 embodiments, R^7 embodiments, R^4 embodiments, R^5 embodiments or with each of the aforementioned R^2 embodiments.

[0090] Another embodiment of the present invention is that group of compounds of formula I wherein s is an integer from zero to four and zero, one or two of R^3 are independently selected from the group consisting of halo, $(C_1$-$C_6)$alkyl, perhalo$(C_1$-$C_6)$alkyl, hydroxy, $(C_1$-$C_6)$alkoxy, perhalo$(C_1$-$C_6)$alkoxy, amino, $(C_1$-$C_6)$alkylamino, $[(C_1$-$C_6)$alkyl$]_2$-amino, -CN, and H_2N(C=O)-. Other embodiments of the present invention include those compounds of formula I (and I(a), I(b), I(c), I(d), I(e), I(f) and I(g)) wherein R^3 is as defined above in combination with each of the aforementioned R^6 embodiments, R^7 embodiments, R^4 embodiments, R^5 embodiments or with each of the aforementioned R^2 embodiments.

[0091] Another embodiment of the present invention is that group of compounds of formula I wherein s is an integer from zero to four and one of R^3 is selected from the group consisting of optionally substituted phenyl, $(C_1$-$C_{10})$heteroaryl, $(C_1$-$C_{10})$heterocyclic and $(C_3$-$C_{10})$cycloalkyl. Other embodiments of the present invention include those compounds of formula I (and I(a), I(b), I(c), I(d), I(e), I(f) and I(g)) wherein R^3 is as defined above in combination with each of the aforementioned R^6 embodiments, R^7 embodiments, R^4 embodiments, R^5 embodiments or with each of the aforementioned R^2 embodiments.

[0092] Another embodiment of the present invention is that group of compounds of formula I wherein s is an integer from zero to four and one of R^3 is selected from the group consisting of hydroxy, $(C_1$-$C_6)$alkoxy, perhalo$(C_1$-$C_6)$alkoxy, phenoxy, $(C_1$-$C_{10})$heteroaryl-O-, $(C_1$-$C_{10})$heterocyclic-O-, $(C_3$-$C_{10})$cycloalkyl-O-, $(C_1$-$C_6)$alkyl-S-, $(C_1$-$C_6)$alkyl-SO_2- and $(C_1$-$C_6)$alkyl-NH-SO_2-. Other embodiments of the present invention include those compounds of formula I (and I(a), I(b), I(c), I(d), I(e), I(f) and I(g)) wherein R^3 is as defined above in combination with each of the aforementioned R^6 embodiments, R^7 embodiments, R^4 embodiments, R^5 embodiments or with each of the aforementioned R^2 embodiments.

[0093] Another embodiment of the present invention is that group of compounds of formula I wherein s is an integer from zero to four and one of R^3 is selected from the group consisting of amino, $(C_1$-$C_6)$alkylamino, $[(C_1$-$C_6)$alkyl$]_2$-amino, $(C_1$-$C_6)$alkyl-SO_2-NH-, $(C_1$-$C_6)$alkyl-(C=O)-NH-, $(C_1$-$C_6)$alkyl-(C=O)-[$((C_1$-$C_6)$alkyl)-N]-, phenyl-(C=O)-NH- and phenyl-(C=O)-[N-$(C_1$-$C_6)$alkyl]-. Other embodiments of the present invention include those compounds of formula I (and I(a), I(b), I(c), I(d), I(e), I(f) and I(g)) wher in R^3 is as defined above in combination with ach of the aforementioned R^6 embodiments, R^7 embodiments, R^4 mbodiments, R^5 embodiments or with each of the aforementioned R^2 embod-

iments.

[0094] Another embodiment of the present invention is that group of compounds of formula I wherein s is an integer from zero to four and one of R^3 is selected from the group consisting of $(C_1$-$C_6)$alkyl-(C=O)-, phenyl-(C=O)-, $(C_1$-$C_{10})$ heteroaryl-(C=O)-, $(C_1$-$C_{10})$heterocyclic-(C=O)-, $(C_3$-$C_{10})$cycloalkyl-(C=O)-, $(C_1$-$C_{10})$heteroaryl-NH-(C=O)-, $(C_1$-$C_{10})$ heterocyclic-NH-(C=O)-, $(C_3$-$C_{10})$cycloalkyl-NH-(C=O)-, HO-(C=O)-, $(C_1$-$C_6)$alkyl-O-(C=O)-, H_2N(C=O)- $(C_1$-$C_6)$ alkyl-NH-(C=O)-, $[(C_1$-$C_6)$alkyl$]_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[((C$_1$-C$_6$)alkyl)-N]-(C=O)- and $(C_1$-$C_6)$ alkyl-(C=O)-O-. Other embodiments of the present invention include those compounds of formula I (and I(a), I(b), I(c), I(d), I(e), I(f) and I(g)) wherein R^3 is as defined above in combination with each of the aforementioned R^6 embodiments, R^7 embodiments, R^4 embodiments, R^5 embodiments or with each of the aforementioned R^2 embodiments.

[0095] Another embodiment of the present invention is that group of compounds of formula I wherein s is an integer from zero to three and each R^3 is independently selected from the group consisting of halo, $(C_1$-$C_6)$alkyl, perhalo $(C_1$-$C_6)$alkyl, hydroxy, $(C_1$-$C_6)$alkoxy, perhalo$(C_1$-$C_6)$alkoxy, -NO_2, amino, $(C_1$-$C_6)$alkylamino, $[(C_1$-$C_6)$alkyl$]_2$-amino, -CN, and H_2N(C=O)-. Other embodiments of the present invention include those compounds of formula I (and I(a), I (b), I(c), I(d), I(e), I(f) and I(g)) wherein R^3 is as defined above in combination with each of the aforementioned R^6 embodiments, R^7 embodiments, R^4 embodiments, R^5 embodiments or with each of the aforementioned R^2 embodiments.

[0096] Preferred compounds of the present invention is that group of compounds of formula I wherein s is an integer from zero to two and each R^3 is independently selected from the group consisting of halo, $(C_1$-$C_6)$alkyl, perhalo$(C_1$-$C_6)$ alkyl, $(C_1$-$C_6)$alkoxy, perhalo$(C_1$-$C_6)$alkoxy and -CN. Other embodiments of the present invention include those compounds of formula I (and I(a), I(b), I(c), I(d), I(e), I(f) and I(g)) wherein R^3 is as defined above in combination with each of the aforementioned R^6 embodiments, R^7 embodiments, R^4 embodiments, R^5 embodiments or with each of the aforementioned R^2 embodiments.

[0097] More preferred compounds of the present invention is that group of compounds of formula I wherein s is an integer from zero to three and each R^3 is independently selected from the group consisting of fluoro, chloro and methyl. Other embodiments of the present invention include those compounds of formula I (and I(a), I(b), I(c), I(d), I(e), I(f) and I(g)) wherein R^3 is as defined above in combination with each of the aforementioned R^6 embodiments, R^7 embodiments, R^4 embodiments, R^5 embodiments or with each of the aforementioned R^2 embodiments.

[0098] An embodiment of the (isoxazole-5-yl)-benzoimidazoles are those compounds wherein R^4 is hydrogen. Another embodiment of the (isoxazole-5-yl)-benzoimidazoles are those compounds wherein R^4 is other than hydrogen.

[0099] Examples of specific preferred compounds of the formula I are the following:

6-[5-(4-fluoro-3-methyl-phenyl)-3H-imidazol-4-yl]-1-isopropyl-1H-benzotriazole;
6-[4-(4-fluoro-phenyl)-oxazol-5-yl]-1-isopropyl-1H-benzotriazole;
6-[5-(4-fluoro-phenyl)-3H-imidazol-4-yl]-1-isopropyl-1H-benzotriazole;
6-[4-(4-fluoro-3-methyl-phenyl)-oxazol-5-yl]-1-isopropyl-1H-benzotriazole;
6-[4-(4-Fluoro-phenyl)-oxazol-5-yl]-1-isopropyl-1H-benzotriazole;
1-Isopropyl-6-(5-phenyl-3H-imidazol-4-yl)-1H-benzotriazole;
1-Isopropyl-6-(4-phenyl-oxazol-5-yl)-1H-benzotriazole;
6-[5-(4-fluoro-3-methyl-phenyl)-3H-imidazol-4-yl]-1-methyl-1H-benzotriazole;
6-[5-(4-fluoro-phenyl)-2-pyridin-3-yl-3H-imidazol-4-yl]-1-isopropyl-1H-benzotriazole; and
6-[5-(4-fluoro-phenyl)-2-pyrazin-2-yl-3H-imidazol-4-yl]-1-isopropyl-1H-benzotriazole.

[0100] Examples of other compounds of the formula I are the following:

6-[5-(4-fluoro-phenyl)-3H-imidazol-4-yl]-1-methyl-1H-benzotriazole;
1-methyl-6-(5-m-tolyl-3H-imidazol-4-yl)-1H-benzotriazole;
1-methyl-6-(5-phenyl-3H-imidazol-4-yl)-1H-benzotriazole;
1-Ethyl-6-(4-m-tolyl-oxazol-5-yl)-1H-benzotriazole;
1-Ethyl-6-(5-m-tolyl-3H-imidazol-4-yl)-1H-benzotriazole;
1-Ethyl-6-[4-(4-fluoro-phenyl)-oxazol-5-yl]-1H-benzotriazole;
1-Ethyl-6-[5-(4-fluoro-phenyl)-3H-imidazol-4-yl]-1H-benzotriazole;
6-[3-benzyl-5-(4-fluoro-3-methyl-phenyl)-3H-imidazol-4-yl]-1-isopropyl-1H-benzotriazole;
6-[5-(4-fluoro-phenyl)-3S-pyrrolidin-3-yl-3H-imidazol-4-yl]-1-isopropyl-1H-benzotriazole mono citrate salt;
6-[5-(4-fluoro-phenyl)-3R-pyrrolidin-3-yl-3H-imidazol-4-yl]-1-isopropyl-1 H-benzotriazole;
1-methyl-6-(2-pyrazin-2-yl-5-m-tolyl-3H-imidazol-4-yl)-1H-benzotriazole;
n-[5-(3-methyl-3H-benzotriazol-5-yl)-4-m-tolyl-1H-imidazol-2-yl]-acetamide;
1-methyl-6-(2-pyridin-3-yl-5-m-tolyl-3H-imidazol-4-yl)-1H-benzotriazole;
1-isopropyl-6-(2-pyridin-3-yl-5-m-tolyl-3H-imidazol-4-yl)-1H-benzotriazole;

6-[4-(3-Chloro-4-fluoro-phenyl)-oxazol-5-yl]-1-isopropyl-1H-benzotriazole;
6-[5-(3-Chloro-4-fluoro-phenyl)-3H-imidazol-4-yl]-1-isopropyl-1H-benzotriazole;
6-[4-(3-Chloro-4-fluoro-phenyl)-thiazol-5-yl]-1-isopropyl-1H-benzotriazole;
6-[3-(3-Chloro-4-fluoro-phenyl)-5-methyl-isoxazol-4-yl]-1-isopropyl-1H-benzotriazole;
6-[3-(3-Chloro-4-fluoro-phenyl)-5-methyl-isothiazol-4-yl]-1-isopropyl-1H-benzotriazole;
6-[3-(3-Chloro-4-fluoro-phenyl)-5-methyl-1H-pyrazol-4-yl]-1-isopropyl-1H-benzotriazole;
6-[2-(3-Chloro-4-fluoro-phenyl)-1H-pyrrol-3-yl]-1-isopropyl-1H-benzotriazole;
6-[5-(2-Chloro-4-fluoro-phenyl)-3H-imidazol-4-yl]-1-isopropyl-1H-benzotriazole;
6-[4-(2-Chloro-4-fluoro-phenyl)-oxazol-5-yl]-1-isopropyl-1H-benzotriazole;
6-[4-(5-Chloro-2-fluoro-phenyl)-oxazol-5-yl]-1-isopropyl-1H-benzotriazole;
6-[5-(5-Chloro-2-fluoro-phenyl)-3H-imidazol-4-yl]-1-isopropyl-1H-benzotriazole;
6-[5-(3-Chloro-phenyl)-3H-imidazoi-4-yl]-1-isopropyl-1H-benzotriazole;
6-[4-(3-Chloro-phenyl)-oxazol-5-yl]-1-isopropyl-1H-benzotriazole;
6-[4-(3,4-Difluoro-phenyl)-oxazol-5-yl]-1-isopropyl-1H-benzotriazole;
6-[5-(3,4-Difluoro-phenyl)-3H-imidazol-4-yl]-1-isopropyl-1H-benzotriazole;
6-[5-(3,4-Difluoro-phenyl)-3H-imidazol-4-yl]-1-phenyl-1H-benzotriazole;
6-[4-(3,4-Difluoro-phenyl)-oxazol-5-yl]-1-phenyl-1H-benzotriazole;
6-[4-(3-Chloro-phenyl)-oxazol-5-yl]-1-phenyl-1H-benzotriazole;
6-[5-(3-Chloro-phenyl)-3H-imidazol-4-yl]-1-phenyl-1H-benzotriazole;
6-[5-(3-Chloro-4-fluoro-phenyl)-3H-imidazol-4-yl]-1-phenyl-1H-benzotriazole;
6-[4-(3-Chloro-4-fluoro-phenyl)-oxazol-5-yl]-1-phenyl-1 H-benzotriazole;
6-[4-(3-Chloro-4-fluoro-phenyl)-oxazol-5-yl]-1-(2-chloro-phenyl)-1H-benzotriazole;
6-[5-(3-Chloro-4-fluoro-phenyl)-3H-imidazol-4-yl]-1-(2-chloro-phenyl)-1H-benzotriazole;
6-[5-(4-Fluoro-phenyl)-3H-imidazol-4-yl]-1-phenyl-1H-benzotriazole;
6-[4-(4-Fluoro-phenyl)-oxazol-5-yl]-1-phenyl-1H-benzotriazole;
1-Phenyl-6-(4-phenyl-oxazol-5-yl)-1H-benzotriazole;
6-[4-(4-Fluoro-3-methyl-phenyl)-oxazol-5-yl]-1-phenyl-1H-benzotriazole;
6-[4-(3-Chloro-4-fluoro-phenyl)-oxazol-5-yl]-1-isobutyl-1H-benzotriazole;
6-[5-(3-Chloro-4-fluoro-phenyl)-3H-imidazol-4-yl]-1-isobutyl-1H-benzotriazole;
6-[5-(2,5-Difluoro-phenyl)-3H-imidazol-4-yl]-1-isopropyl-1 H-benzotriazole;
6-[4-(2,5-Difluoro-phenyl)-oxazol-5-yl]-1-isopropyl-1H-benzotriazole;
6-[4-(3-Bromo-4-fluoro-phenyl)-oxazol-5-yl]-1-isopropyl-1H-benzotriazole;
6-[5-(3-Bromo-4-fluoro-phenyl)-3H-imidazol-4-yl]-1-isopropyl-1H-benzotriazole;
6-[5-(2,4-Difluoro-phenyl)-3H-imidazol-4-yl]-1-isopropyl-1H-benzotriazole;
6-[4-(2,4-Difluoro-phenyl)-oxazol-5-yl]-1-isopropyl-1H-benzotriazole;
4-Phenyl-5-(3-phenyl-3H-benzotriazol-5-yl)-1H-imidazole-2-carboxylic acid amide;
4-(4-Fluoro-phenyl)-5-(3-phenyl-3H-benzotriazol-5-yl)-1H-imidazole-2-carboxylic acid amide;
4-(3-Chloro-phenyl)-5-(3-phenyl-3H-benzotriazol-5-yl)-1H-imidazole-2-carboxylic acid amide;
4-(3-Chloro-phenyl)-5-(3-phenyl-3H-benzotriazol-5-yl)-1H-imidazole-2-carboxylic acid;
1-[4-(3-Chloro-phenyl)-5-(3-phenyl-3H-benzotriazol-5-yl)-1H-imidazol-2-yl]-ethanone;
1-[5-(3-Phenyl-3H-benzotriazol-5-yl)-4-m-tolyl-1H-imidazol-2-yl]-ethanone;
5-(3-Phenyl-3H-benzotriazol-5-yl)-4-m-tolyl-1H-imidazole-2-carboxylic acid;
5-(3-Phenyl-3H-benzotriazol-5-yl)-4-m-tolyl-1H-imidazole-2-carboxylic acid amide;
5-(3-Phenyl-3H-benzotriazol-5-yl)-4-m-tolyl-1H-imidazole-2-carboxylic acid methyl ester;
[5-(3-Phenyl-3H-benzotriazol-5-yl)-4-m-tolyl-1H-imidazol-2-yl]-urea;
[4-(3-Chloro-phenyl)-5-(3-phenyl-3H-benzotriazol-5-yl)-1H-imidazol-2-yl]-urea;
4-(3-Chloro-phenyl)-5-(3-phenyl-3H-benzotriazol-5-yl)-1H-imidazole-2-carboxylic acid methyl ester; and
5-[3-(2-Chloro-phenyl)-3H-benzotriazol-5-yl]-4-m-tolyl-1H-imidazole-2-carboxylic acid amide.

[0101] The present invention also includes isotopically-labelled compounds, which are identical to those recited in Formula I, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the pres nt invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-

14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of Formula I of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

[0102] The compounds of Formula I or a pharmaceutically acceptable salt thereof can be used in the manufacture of a medicament for the prophylactic or therapeutic treatment of any disease state in a human, or other mammal, which is exacerbated or caused by excessive or unregulated cytokine production by such mammal's cells, such as but not limited to monocytes and/or macrophages.

[0103] Compounds of Formula (I) are capable of inhibiting proinflammatory cytokines, such as IL-1, IL-6, IL-8, and TNF and are therefore of use in therapy. IL-1, IL-6, IL-8 and TNF affect a wide variety of cells and tissues and these cytokines, as well as other leukocyte-derived cytokines, are important and critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these pro-inflammatory cytokines is of benefit in controlling, reducing and alleviating many of these disease states.

[0104] Accordingly, the present invention provides a method of treating a cytokine mediated disease which comprises administering an effective cytokine-interfering amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0105] Certain compounds of Formula (I) are capable of inhibiting inducible pro-inflammatory proteins, such as COX-2, also referred to by many other names such as prostaglandin endoperoxide synthase-2 (PGHS-2) and are therefore of use in therapy. These proinflammatory lipid mediators of the cyclooxygenase (COX) pathway are produced by the inducible COX-2 enzyme. Regulation, therefore of COX-2 which is responsible for these products derived from arachidonic acid, such as prostaglandins, affect a wide variety of cells and tissues. Expression of COX-1 is not effected by compounds of Formula (I). This selective inhibition of COX-2 is accepted as alleviating or sparing ulcerogenic liability associated with inhibition of COX-1 thereby inhibiting prostoglandins essential for cytoprotective effects. Thus inhibition of these pro-inflammatory mediators is of benefit in controlling, reducing and alleviating many of these disease states. Most notably these inflammatory mediators, in particular prostaglandins, have been implicated in pain, such as in the sensitization of pain receptors, or edema. This aspect of pain management, therefore, includes treatment of neuromuscular pain, headache, cancer pain, and arthritis pain. Compounds of Formula (I), or a pharmaceutically acceptable salt thereof, are of use in therapy in a human, or other mammal, by inhibition of the synthesis of the COX-2 enzyme.

[0106] Accordingly, the present invention provides a method of inhibiting the synthesis of COX-2 which comprises administering an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof. The present invention also provides for a method of treatment in a human, or other mammal, by inhibition of the synthesis of the COX-2 enzyme.

[0107] In particular, compounds of Formula (I) or a pharmaceutically acceptable salt thereof are of use in the therapy of any disease state in a human, or other mammal, which is exacerbated by or caused by excessive or unregulated IL-1, IL-8 or TNF production by such mammal's cells, such as, but not limited to, monocytes and/or macrophages.

[0108] Accordingly, in another aspect, this invention relates to a method of inhibiting the production of IL-1 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0109] There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These disease states include rheumatoid arthritis, osteoarthritis, meningitis, ischemic and hemorrhagic stroke, neurotrauma/closed head injury, stroke, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease, tuberculosis, atherosclerosis, muscle degeneration, multiple sclerosis, cachexia, bone resorption, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis. Recent evidence also links IL-1 activity to diabetes, pancreatic β cells disease, and Alzheimer's disease.

[0110] Use of a p38 inhibitor for the treatment of p38 mediated disease states, can include, but is not limited to neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and multiple sclerosis, etc.. In a further aspect, this invention relates to a method of inhibiting the production of TNF in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0111] Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, stroke, cerebral malaria, chronic obstructive pulmonary disease, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption diseases, such as osteoporosis, cardiac, brain and renal reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, (including HIV-

induced forms), cerebral malaria, meningitis, ischemic and hemorrhagic stroke, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, or ARC (AIDS related complex), keloid formation, scar tissue formation, inflammatory bowel disease, Crohn's disease, ulcerative colitis and pyresis.

[0112] Compounds of Formula (I) are also useful in the treatment of viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. The viruses contemplated for treatment herein are those that produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibiting-compounds of Formula (I). Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3, Cytomegalovirus (CMV), Influenza, adenovirus and the Herpes group of viruses, such as but not limited to, Herpes Zoster and Herpes Simplex. Accordingly, in a further aspect, this invention relates to a method of treating a mammal afflicted with a human immunodeficiency virus (HIV) which comprises administering to such mammal an effective TNF inhibiting amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0113] Compounds of Formula (I) may also be used in association with the veterinary treatment of mammals, other than in humans, in need of inhibition of TNF production. TNF mediated diseases for treatment, in animals include disease states such as those noted above, but in particular viral infections. Examples of such viruses include, but are not limited to, lentivirus infections such as, equine infectious anaemia virus, caprine arthritis virus, visna virus, or maedi virus or retrovirus infections, such as but not limited to feline immunodeficiency virus (FIV), bovine immunodeficiency virus, or canine immunodeficiency virus or other retroviral infections.

[0114] The compounds of Formula (I) may also be used topically in the treatment of topical disease states mediated by or exacerbated by excessive cytokine production, such as by IL-1 or TNF respectively, such as inflamed joints, eczema, contact dermatitis psoriasis and other inflammatory skin conditions such as sunburn; inflammatory eye conditions including conjunctivitis; pyresis, pain and other conditions associated with inflammation. Periodontal disease has also been implemented in cytokine production, both topically and systemically. Hence, the use of compounds of Formula (I) to control the inflammation associated with cytokine production in such peroral diseases such as gingivitis and periodontitis is another aspect of the present invention.

[0115] Compounds of Formula (I) have also been shown to inhibit the production of IL-8 (Interleukin-8, NAP). Accordingly, in a further aspect, this invention relates to a method of inhibiting the production of IL-8 in a mammal in need thereof which comprises administering, to said mammal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0116] There are many disease states in which excessive or unregulated IL-8 production is implicated in exacerbating and/or causing the disease. These diseases are characterized by massive neutrophil infiltration such as, psoriasis, inflammatory bowel disease, asthma, cardiac and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis. All of these diseases are associated with increased IL-8 production which is responsible for the chemotaxis of neutrophils into the inflammatory site. In contrast to other inflammatory cytokines (IL-1, TNF, and IL-6), IL-8 has the unique property of promoting neutrophil chemotaxis and activation. Therefore, the inhibition of IL-8 production would lead to a direct reduction in the neutrophil infiltration.

[0117] The compounds of Formula (I) are administered in an amount sufficient to inhibit a cytokine, in particular IL-1, IL-6, IL-8 or TNF, production such that it is regulated down to normal levels, or in some case to subnormal levels, so as to ameliorate or prevent the disease state. Abnormal levels of IL-1, IL-6, IL-8 or TNF, for instance in the context of the present invention, constitute: (i) levels of free (not cell bound) IL-1, IL-6, IL-8 or TNF greater than or equal to 1 picogram per ml; (ii) any cell associated IL-1, IL-6, IL-8 or TNF; or (iii) the presence of IL-1, IL-6, IL-8 or TNF mRNA above basal levels in cells or tissues in which IL-1, IL-6, IL-8 or TNF, respectively, is produced.

[0118] The discovery that the compounds of Formula (I) are inhibitors of cytokines, specifically IL-1. IL-6, IL-8 and TNF is based upon the effects of the compounds of Formula (I) on the production of the IL- 1, IL-8 and TNF in *in vitro* assays which are described herein or are well known to those skilled in the art.

[0119] As used herein, the term "inhibiting the production of IL-1 (IL-6, IL-8 or TNF)" refers to:

a) a decrease of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels by inhibition of the *in vivo* release of the cytokine by all cells, including but not limited to monocytes or macrophages;

b) a down regulation, at the genomic level, of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels;

c) a down regulation, by inhibition of the direct synthesis of the cytokine (IL-1, IL-6, IL-8 or TNF) as a postranslational event to normal or sub-normal levels; or

d) a down regulation, at the translational level, of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels.

[0120] As us d herein, the term "TNF mediated disease or disease state" refers to any and all disease states in

which TNF plays a role, either by production of TNF itself, or by TNF causing another monokine to be released, such as but not limited to IL- 1, IL-6 or IL-8. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF.

[0121] As used herein, the term "cytokine" refers to any secreted polypeptide that affects the functions of cells and is a molecule which modulates interactions between cells in the immune, inflammatory or hematopoietic response. A cytokine includes, but is not limited to, monokines and lymphokines, regardless of which cells produce them. For instance, a monokine is referred to as being produced and secreted by a mononuclear cell, such as a macrophage and/or monocyte. Many other cells however also produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epideral keratinocytes and B-lymphocytes. Lymphokines are generally referred to as being produced by lymphocyte cells. Examples of cytokines include, but are not limited to Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-alpha (TNF-α) and Tumor Necrosis Factor beta (TNF-β).

[0122] As used herein, the term "cytokine interfering" or "cytokine suppressive amount" refers to an effective amount of a compound of Formula (I) which will cause a decrease in the *in vivo* levels of the cytokine to normal or sub-normal levels, when given to a patient for the treatment of a disease state which is exacerbated by, or caused by, excessive or unregulated cytokine production.

[0123] As used herein, the cytokine referred to in the phrase "inhibition of a cytokine for use in the treatment of a HIV-infected human" is a cytokine which is implicated in (a) the initiation and/or maintenance of T cell activation and/or activated T cell-mediated HIV gene expression and/or replication and/or (b) any cytokine-mediated disease associated problem such as cachexia or muscle degeneration.

[0124] As TNF-β (also known as lymphotoxin) has close structural homology with TNF-α (also known as cachectin) and since each induces similar biologic responses and binds to the same cellular receptor, both TNF-α and TNF-β are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise.

[0125] A relatively new member of the MAP kinase family, alternatively termed CSBP, p38 or RK, has been identified by several laboratories [See Lee et al., Nature, Vol. 300, n(72), 739-746 (1994)]. Activation of this protein kinase via dual phosphorylation has been observed in different cell systems upon stimulation by a wide spectrum of stimuli, such as physicochemical stress and treatment with lipopolysaccharide or proinflammatory cytokines such as interleukin-1 and tumor necrosis factor. The cytokine biosynthesis inhibitors, of the, present invention, compounds of Formula (I) have been determined to be potent and selective inhibitors of CSBP/p38/RK kinase activity, These inhibitors are of aid in determining the signaling pathways involvement in inflammatory responses. In particular, a definitive signal transduction pathway can be prescribed to the action of lipopolysaccharide in cytokine production in macrophages. In addition to those diseases already noted herein, treatment of stroke, neurotrauma/CNS head injury, cardiac, brain and renal reperfusion injury, thrombosis, glomerulonephritis, diabetes and pancreatic β cells, multiple sclerosis, muscle degeneration , eczema, psoriasis, sunburn, and conjunctivitis are also included.

[0126] The cytokine inhibitors were subsequently tested in a number of animal models for anti-inflammatory activity. Model systems were chosen that were relatively insensitive to cyclooxygenase inhibitors in order to reveal the unique activities of cytokine suppressive agents. The inhibitors exhibited significant activity in many such *in vivo* studies. Most notable are its effectiveness in the collagen-induced arthritis model and inhibition of TNF production in the endotoxic shock model. In the latter study, the reduction in plasma level of TNF correlated with survival and protection from endotoxic shock related mortality. Also of great importance are the compound's effectiveness in inhibiting bone resorption in a rat fetal long bone organ culture system. Griswold et al., (1988) Arthritis Rheum. 31:1406-1412; Badger, et al., (1989) Circ. Shock *27, 51-61,* Votta et al., (1994) *in vitro.* Bone *15,* 533-538; Lee et al., (1993.). B Ann. N. Y. Acad. Sci. *696,* 149-170.

[0127] It is also recognized that both IL-6 and IL-8 are produced during rhinovirus (HRV) infections and contribute to the pathogenesis of common cold and exacerbation of asthma associated with HRV infection (Turner et al., (1998), Clin. Infec. Dis., Vol. 26, p. 840; Teren et al. (1997), Am. J. Respir. Crit. Care Med., Vol. 155, p. 1362; Grunberg et al. (1997), Am. J. Respir. Crit. Care Med., Vol. 156, p. 609 and Zhu et al., J. Clin. Invest. (1996), Vol. 97, p 421). It has also been demonstrated *in vitro* that infection of pulmonary epithelial cells with HRV results in production of IL-6 and IL-8 (Subauste et al., J. Clin. Invest. (1995), Vol. 96, p. 549). Epithelial cells represent the primary site of infection of HRV. Therefore, another aspect of the present invention is a method of treatment to reduce inflammation associated with a rhinovirus infection, not necessarily a direct effect of the virus itself.

[0128] Another aspect of the present invention involves the novel use of these p38/cytokine inhibitors for the treatment of chronic inflammatory or proliferative or angiogenic diseases, which are caused by excessive, or inappropriate angiogenesis.

[0129] Chronic diseases which have an inappropriate angiogenic component are various ocular neovasularizations, such as diabetic retinopathy and macular degeneration. Other chronic dis ases which have an excessive or increased

proliferation of vasculature are tumor growth and metastasis, atherosclerosis and certain arthritic conditions. Therefore, cytokine inhibitors will be of utility in the blocking of the angiogenic component of these disease states.

[0130] The term "excessive or increased proliferation of vasculature inappropriate angiogenesis" as used herein includes, but is not limited to, diseases which are characterized by hemangiomas and ocular diseases.

[0131] The term "inappropriate angiogenesis" as used herein includes, but is not limited to, diseases which are characterized by vesicle proliferation with accompanying tissue proliferation, such as occurs in cancer, metastasis, arthritis and atherosclerosis.

[0132] This invention also encompasses methods of treating or preventing disorders that can be treated or prevented by the inhibition of ERK/MAP in a mammal, preferably a human, comprising administering to said mammal an effective amount of a compound of the formula I.

[0133] Accordingly, the present invention provides a method of treating a p38 kinase mediated disease in a mammal in need thereof, preferably a human, which comprises administering to said mammal, an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0134] Preferred p38 mediated diseases for treatment include, but are not limited to psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, Alzheimer's disease, stroke, ischemic and hemorrhagic stroke, neurotrauma/closed head injury, asthma, adult respiratory distress syndrome, chronic obstructive pulmonary disease, cerebral malaria, meningitis, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcostosis, bone resorption disease, osteoporosis, restenosis, cardiac reperfusion injury, brain and renal reperfusion injury, chronic renal failure, thrombosis, glomerularonephritis, diabetes, diabetic retinopathy, macular degeneration, graft vs. host reaction, allograft rejection, inflammatory bowel disease, Crohn's disease, ulcerative colitis, neurodegenerative disease, multiple sclerosis, muscle degeneration, diabetic retinopathy, macular degeneration, tumor growth and metastasis, angiogenic disease, rhinovirus infection, peroral disease, such as gingivitis and periodontitis, eczema, contact dermatitis, psoriasis, sunburn, and conjunctivitis.

[0135] The term "treating", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment, as used herein, refers to the act of treating, as "treating" is defined immediately above.

[0136] This invention also encompasses pharmaceutical compositions for the treatment of a condition selected from the group consisting of arthritis, psoriatic arthritis, Reiter's syndrome, gout, traumatic arthritis, rubella arthritis and acute synovitis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, Alzheimer's disease, stroke, neurotrauma, asthma, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcososis, bone resorption disease, osteoporosis, restenosis, cardiac and renal reperfusion injury, thrombosis, glomerularonephritis, diabetes, graft vs. host reaction, allograft rejection, inflammatory bowel disease, Crohn's disease, ulcerative colitis, multiple sclerosis, muscle degeneration, eczema, contact dermititis, psoriasis, sunburn, or conjunctivitis shock in a mammal, including a human, comprising an amount of a compound of formula I effective in such treatment and a pharmaceutically acceptable carrier.

[0137] This invention also encompasses pharmaceutical compositions for the treatment of a condition which can be treated by the inhibition of ERK/MAP kinase in a mammal, including a human, comprising an amount of a compound of formula I effective in such treatment and a pharmaceutically acceptable carrier.

[0138] This invention also encompasses pharmaceutical compositions for the treatment of a condition which can be treated by the inhibition of p38 kinase in a mammal, including a human, comprising an amount of a compound of formula I effective in such treatment and a pharmaceutically acceptable carrier.

[0139] This invention also encompasses pharmaceutical compositions containing prodrugs of compounds of the formula I. Compounds of formula I having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues which are covalently joined through peptide bonds to free amino, hydroxy or carboxylic acid groups of compounds of formula I. The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters which are covalently bonded to the above substituents of formula I through the carbonyl carbon prodrug sidechain.

[0140] The present invention also encompasses sustained release compositions.

[0141] The present invention also relates to processes of preparing the compounds of formula I and intermediates used in such processes.

[0142] One of ordinary skill in the art will appreciate that the compounds of the invention ar useful in treating a diverse array of diseases. One of ordinary skill in the art will also appreciate that when using the compounds of the

invention in the treatment of a specific disease that th compounds of the invention may be combined with various existing therapeutic agents used for that disease.

[0143] For the treatment of rheumatoid arthritis, the compounds of the invention may be combined with agents such as TNF-α inhibitors such as anti-TNF monoclonal antibodies (such as Remicade, CDP-870 and D_2E_7) and TNF receptor immunoglobulin molecules (such as Enbrel®), COX-2 inhibitors (such as meloxicam, celecoxib , rofecoxib, valdecoxib and etoricoxib) low dose methotrexate, leflunomide, hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold.

[0144] The compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors such as celecoxib, valdecoxib, rofecoxib and etoricoxib, analgesics and intraarticular therapies such as corticosteroids and hyaluronic acids such as hyalgan and synvisc.

[0145] The compounds of the present invention may also be used in combination with anticancer agents such as endostatin and angiostatin or cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and alkaloids, such as vincristine, farnesyl transferase inhibitors, VegF inhibitors, and antimetabolites such as methotrexate.

[0146] The compounds of the invention may also be used in combination with antiviral agents such as Viracept, AZT, aciclovir and famciclovir, and antisepsis compounds such as Zovant, tifacogin, NOX-100 and GR270773.

[0147] The compounds of the present invention may also be used in combination with cardiovascular agents such as calcium channel blockers, lipid lowering agents such as statins, fibrates, beta-blockers, Ace inhibitors, Angiotensin-2 receptor antagonists and platelet aggregation inhibitors.

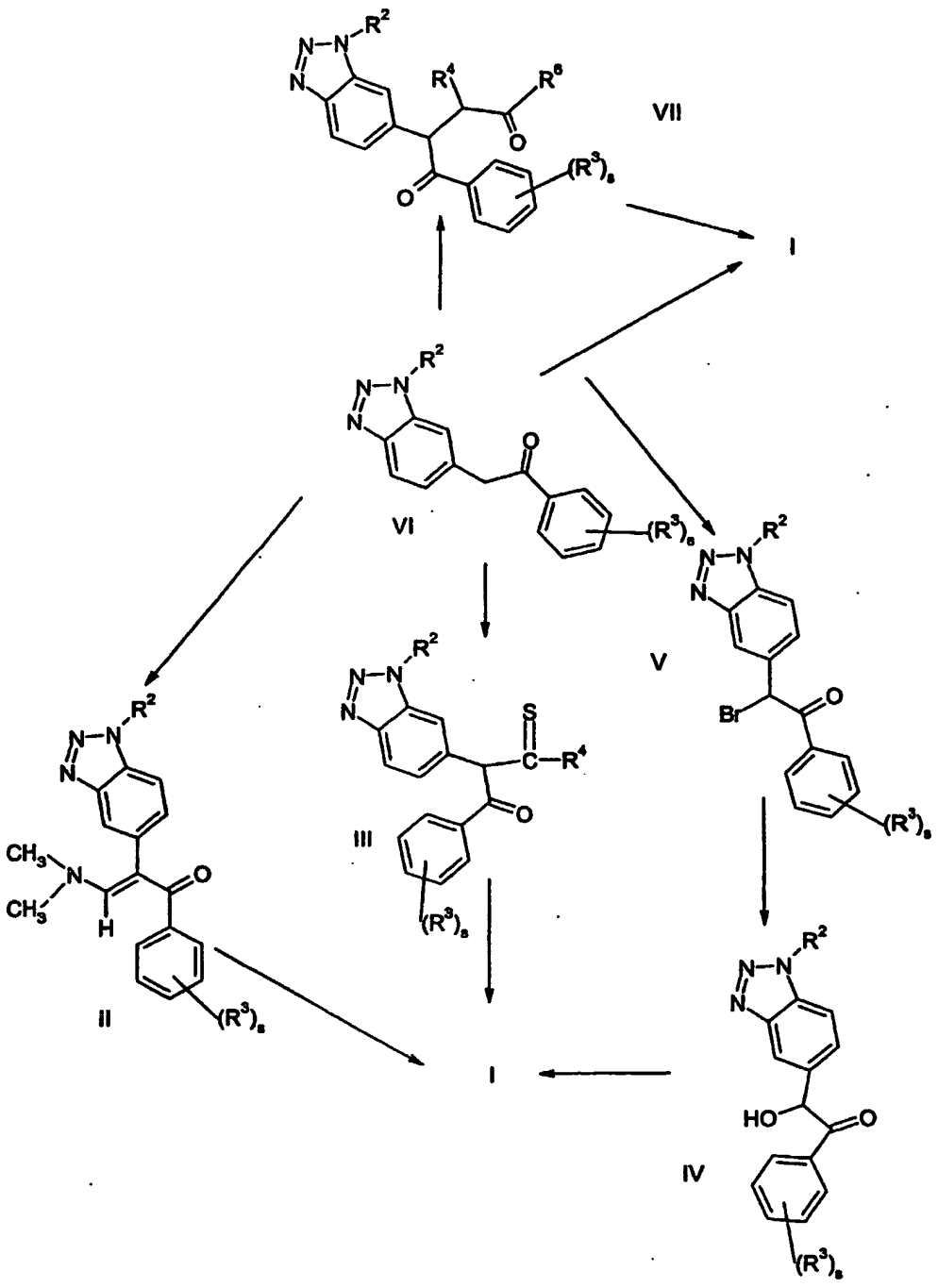
[0148] The compounds of the present invention may also be used in combination with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as deprenyl, L-dopa, Requip, Mirapex, MAOB inhibitors such as selegine and rasagiline, comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, Nicotine agonists, Dopamine agonists and inhibitors of neuronal nitric oxide synthase), and anti-Alzheimer's drugs such as donepezil, tacrine, COX-2 inhibitors, propentofylline or metryfonate.

[0149] The compounds of the present invention may also be used in combination with osteoporosis agents such as roloxifene, droloxifene, lasofoxifene or fosomax and immunosuppressant agents such as FK-506 and rapamycin.

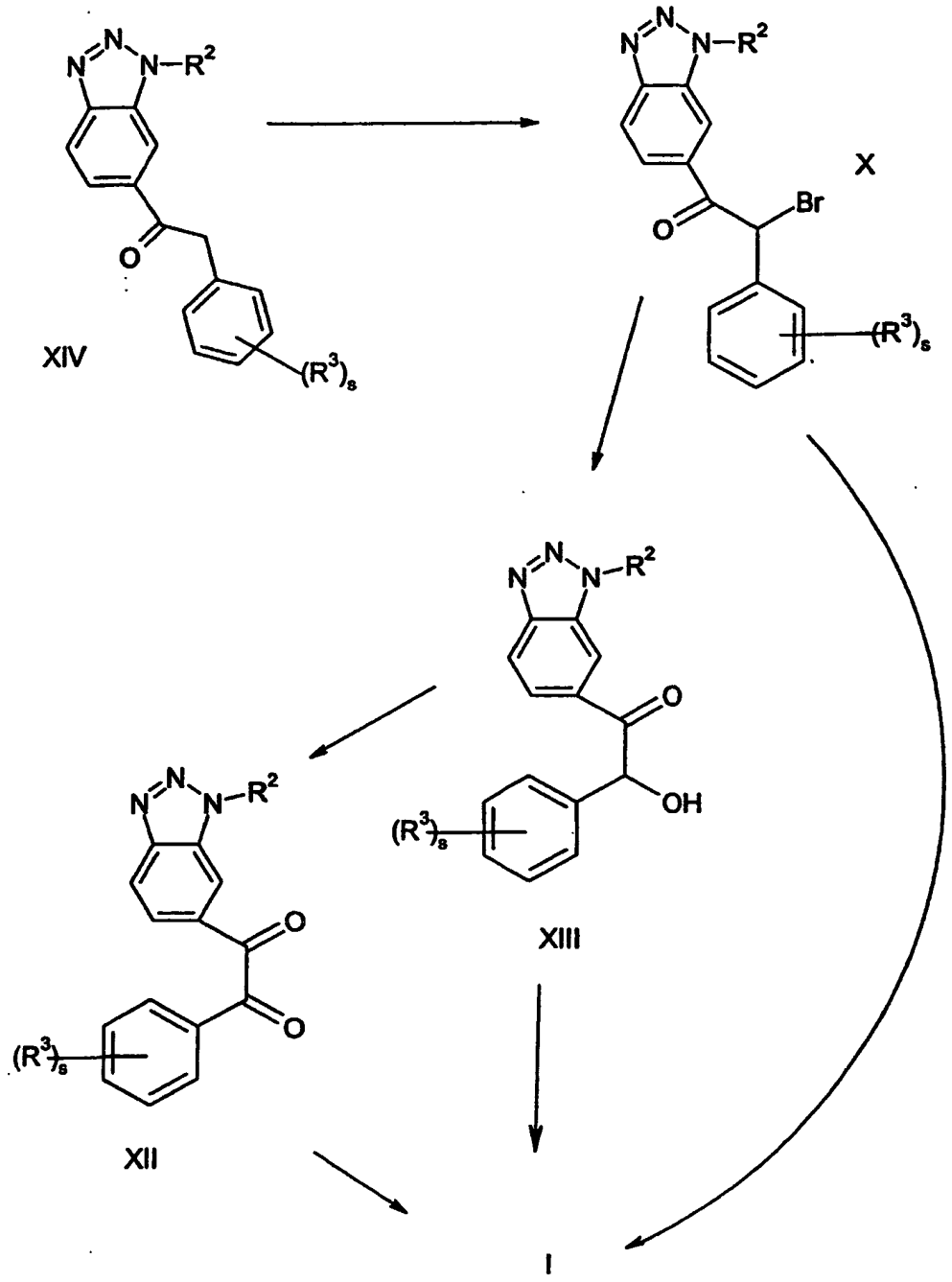
Detailed Description of the Invention

[0150] Compounds of the formula I may be prepared according to the following reaction schemes and discussion. Unless otherwise indicated, m, n, p, s, B, R^2 through R^{16} and Het and structural formula I in the reaction schemes and discussion that follow are as defined above.

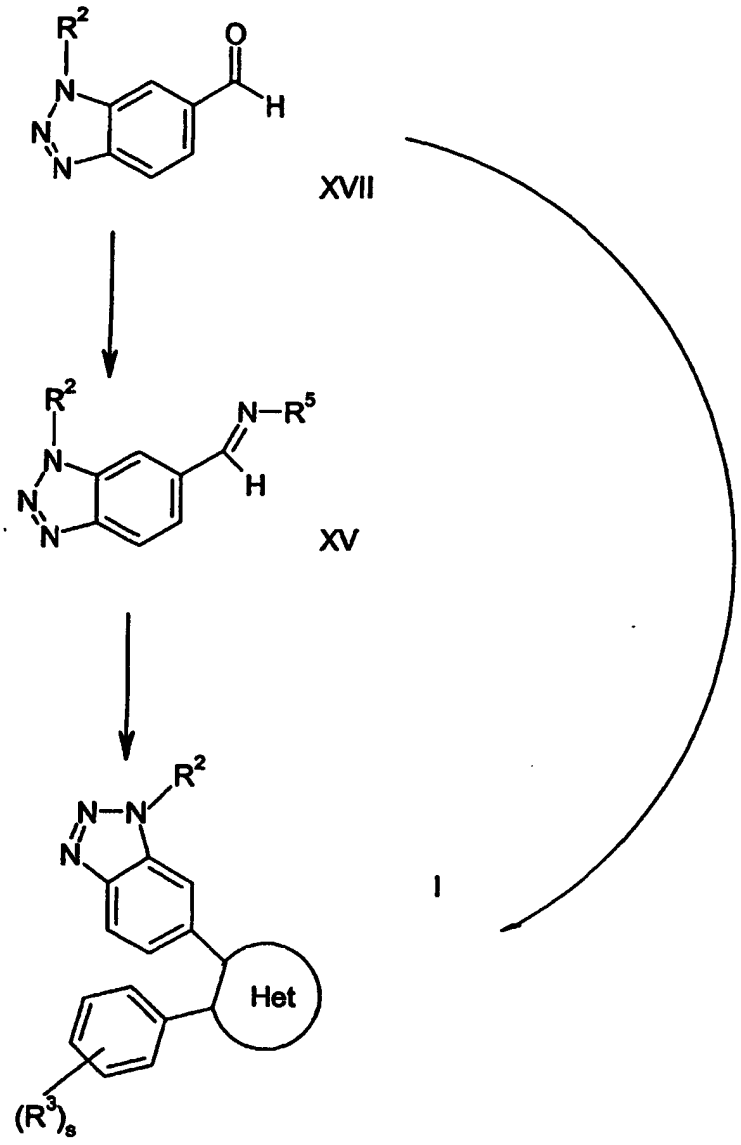
Scheme 1



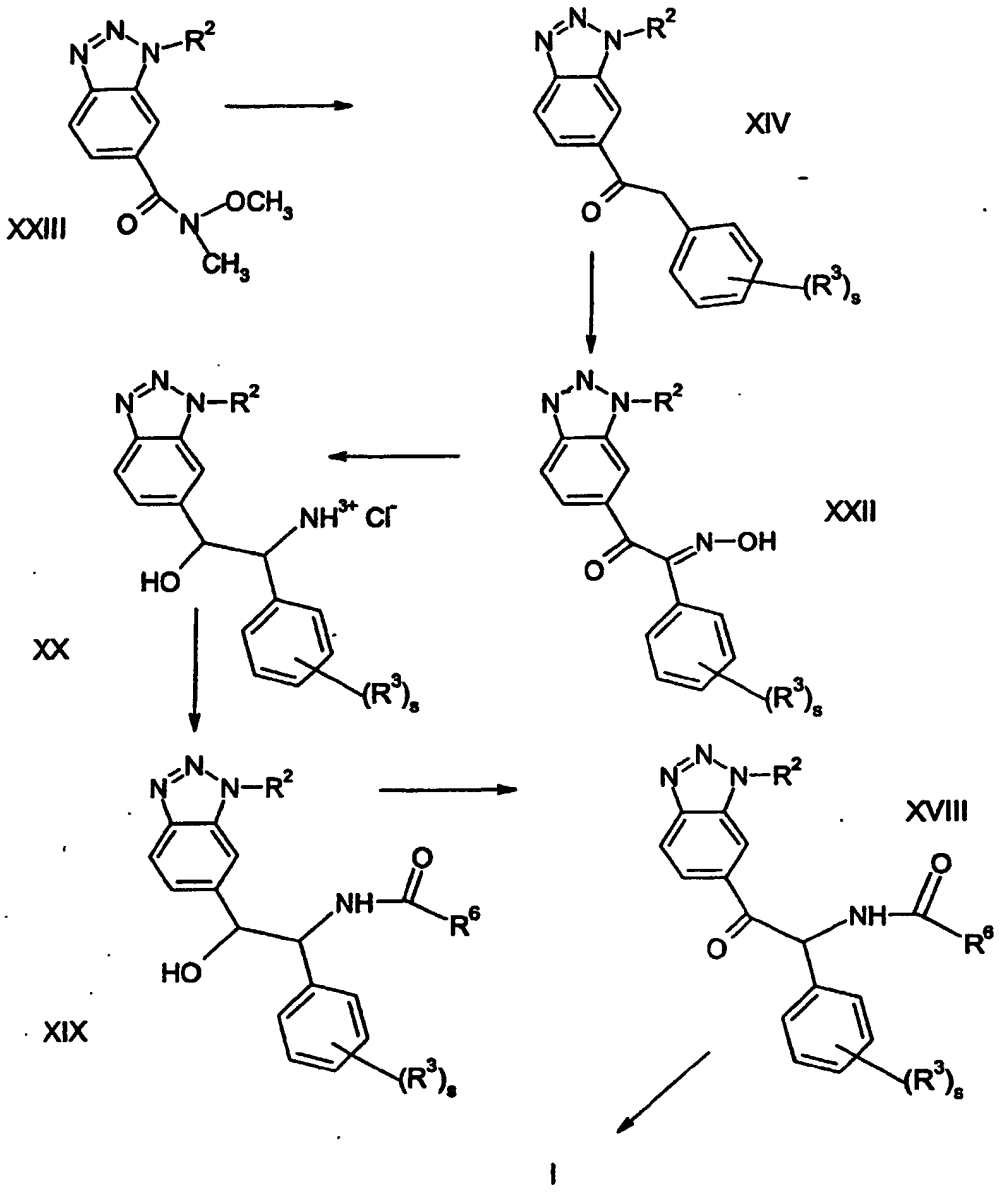
Scheme 2



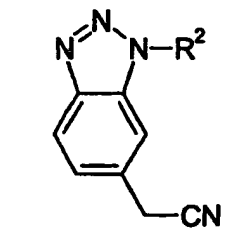
Scheme 3



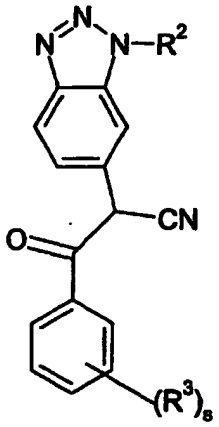
Scheme 4



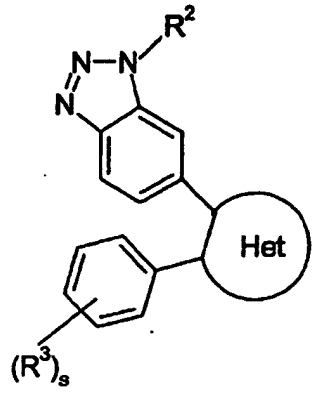
Scheme 5



XXV

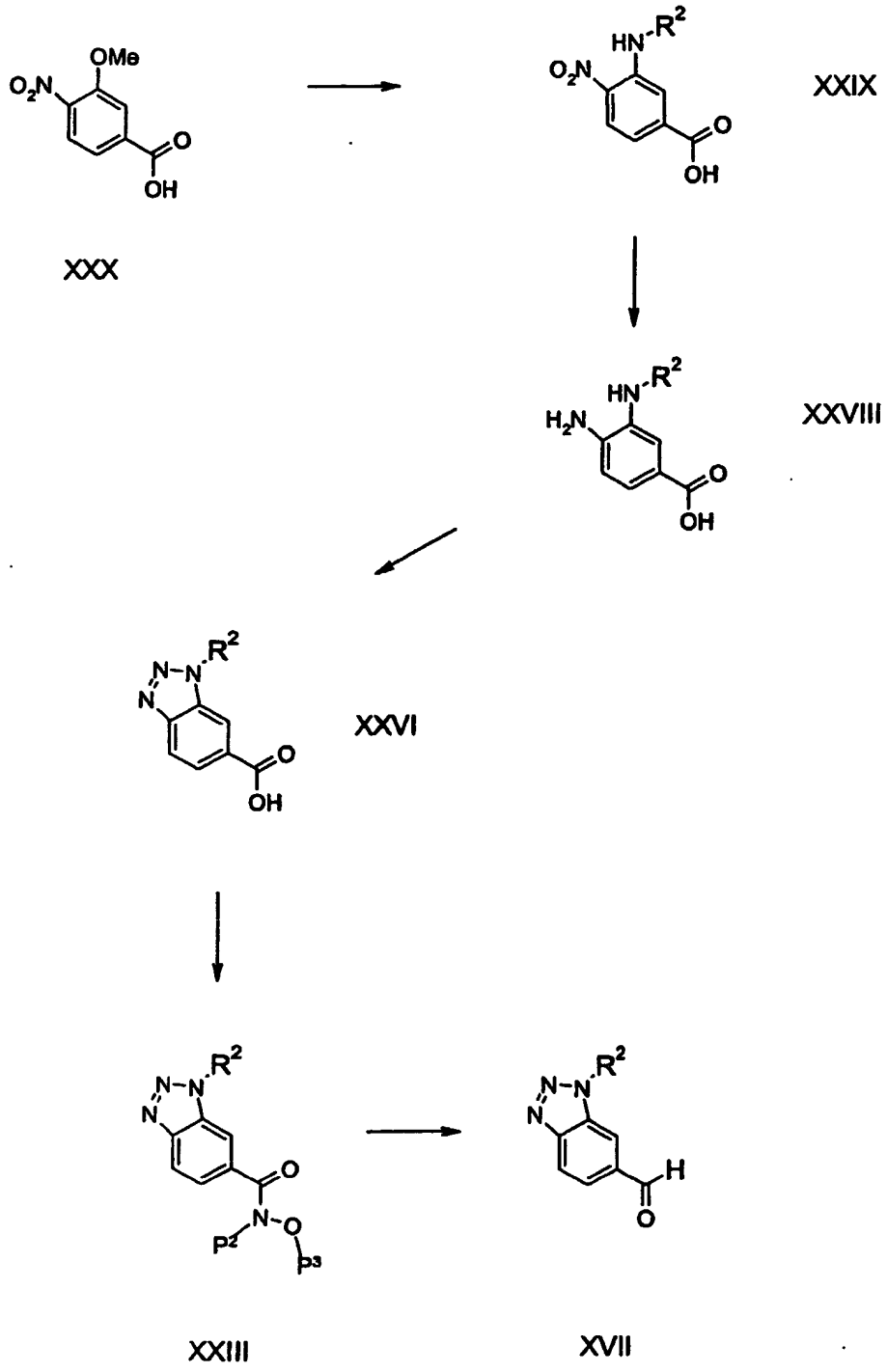


XXIV

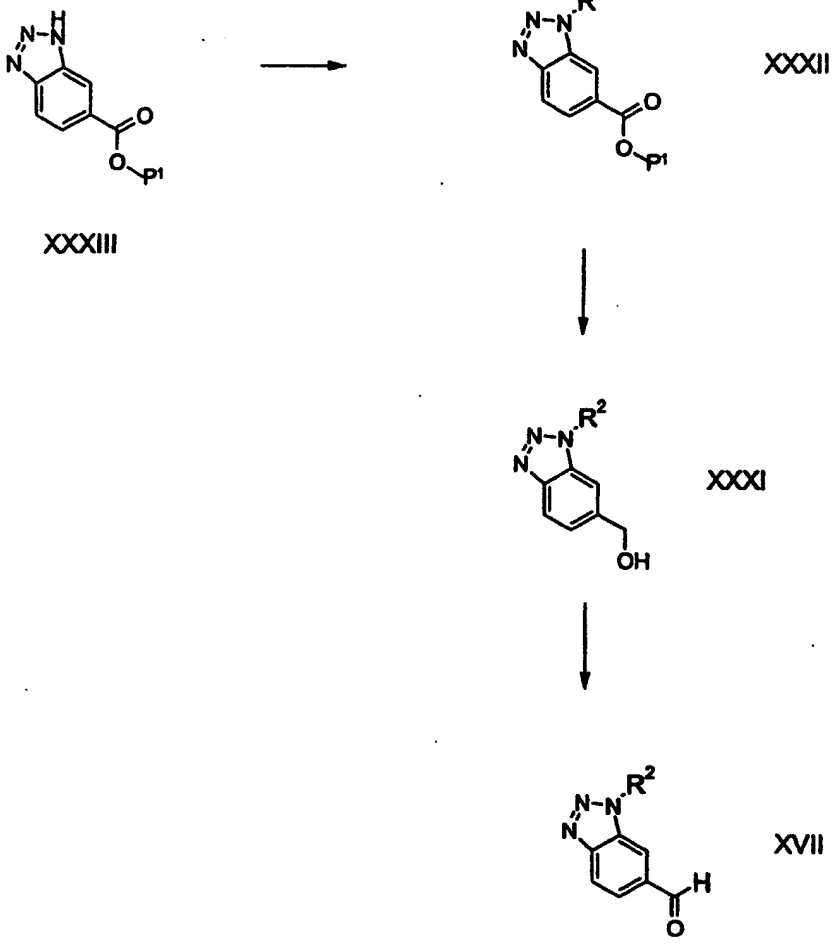


I

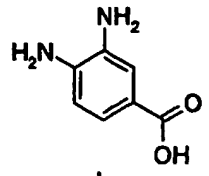
Scheme 6


OMe
O_2N
O
OH
XXX
HN-R^2
O_2N
XXIX
H_2N
XXVIII
N-N-R^2
XXVI
P^2
N-O
P^3
H
XXIII
XVII

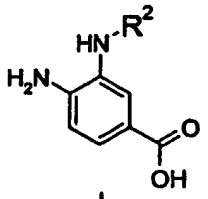
Scheme 7



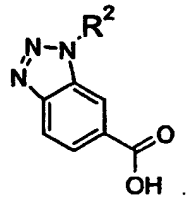
Scheme 8



XXXI



XXVIII



XXVI

[0151] Scheme 1 refers to the preparation of compounds of the formula I. Referring to Scheme 1, a compound of the formula I, wherein $(R^3)_s$-phenyl-Het is (c) or (f), can be prepared from compounds of the formula II by reaction with an aminating reagent. Suitable aminating reagents include hydrazines of the formula H_2N-NH-R^7, in a polar solvent. Suitable solvents include alcohols such as ethanol, propanol or butanol or mixtures of alcohols and acetic acid, preferably ethanol. The aforesaid reaction is conducted at a temperature of about 10°C to about 30°C, preferably at about 22°C, for a period from about 1 hour to about 7 hours, preferably about 3 hours.

[0152] The compound of formula II is prepared from a compound of formula VI by reaction with an acetal, such as dimethylformamide - dimethylacetal, at a temperature of about 60°C to about 90°C, preferably about 80°C for a period from about 1 hour to about 6 hours, preferably about 3 hours.

[0153] Alternatively, compounds of the formula I, wherein $(R^3)_s$-phenyl-Het is (c) or (f), can be prepared from compounds of the formula III by reaction with an aminating reagent such as H_2N-NH-R^7 according to methods analogous to the conversion of compounds of formula II to formula I, above.

[0154] The compound of formula III is prepared from a compound of formula VI by reaction with an isothiocyanate. Suitable isothiocyanates include compounds of the formula R^4-N=C=S. Reactions with isothiocyanates are facilitated by the addition of a base, such as sodium hydride, lithium diisopropylamide or other suitable strong bases. Suitable solvents for the aforesaid reaction include pyridine, N,N-dimethylformamide or tetrahydrofuran, preferably pyridine. The aforesaid reaction is performed from a period of about 0.5 hour to about 4 hours at a temperature of about 0°C to about 30°C. The deprotonation reaction with above said bases is followed by the addition of a suitable isothiocyanate

and is performed for a period from about 10 minutes to about 20 hours, at a temperature of about 0°C to about 30°C, preferably about 22°C for a period from about 0.5 hour to about 24 hours.

[0155] Compounds of the formula I, wherein $(R^3)_s$-phenyl-Het is (b), can be prepared from compounds of the formula IV, by reaction with an aldehyde of the formula R^6-(C=O)H in the presence of an ammonia source and cuprous acetate and a polar solvent. Suitable ammonia sources include ammonium trifluoroacetate, ammonia, and ammonium acetate, preferably ammonium acetate. The aforesaid reaction can be run neat or in the presence of a solvent such as alcohols (methanol, ethanol or butanol) and acetic acid. The aforesaid reaction can be run at a temperature from about 20°C to about 80°C for a period from about 15 minutes to about 4 hours, preferably neat conditions at about 60°C for about 2 hours.

[0156] Compounds of the formula I, wherein $(R^3)_s$-phenyl-Het is (d) can be prepared from compounds of the formula IV, by reaction with an acylating reagent of the formula $R^6(C=O)$-L, wherein L is a leaving group such as halo or anhydrido, using method well known to those skilled in the art. The acyl derivative, so formed, is converted to the compound of formula I by cyclodehydration in the presence of a source of ammonia. Suitable solvents include acetic acid and tetrahydrofuran. The aforesaid reaction can be run at a temperature from about 22°C to about 80°C, preferably 50°C, for a period from about 1 hour to about 24 hours, preferably 2 hours.

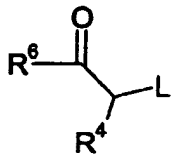
[0157] The compound of formula IV is prepared from a compound of formula V by reaction with sodium methoxide, or sodium ethoxide, or sodium tert-butoxide, preferably sodium methoxide, in an alcohol solvent, such as methanol, ethanol, isopropanol, preferably methanol. The aforesaid reaction can be conducted at a temperature of about 0°C to about 30°C, preferably at about 22°C, for a period of time from 15 minutes to about 3 hours, preferably about 30 minutes. The aforesaid reaction is followed by an aqueous acidic work-up.

[0158] The compound of formula V is prepared from a compound of formula VI by reaction with bromine (Br_2) in a polar solvent. Suitable solvents include acetic acid, chloroform or methylene chloride, preferably acetic acid. The aforesaid reaction is conducted at a temperature of about 0°C to about 30°C preferably at about 22°C (room temperature) for a period from about 10 minutes to about 4 hours, preferably about 30 minutes.

[0159] Compounds of the formula I, wherein $(R^3)_s$-phenyl-Het is (a), can be prepared from compounds of the formula VII, by reaction with an ammonia source and cuprous acetate and a polar solvent. Suitable ammonia sources include ammonium trifluoroacetate, ammonia, and ammonium acetate, preferably ammonium acetate. The aforesaid reaction can be run neat or in the presence of a solvent such as alcohols (methanol, ethanol or butanol) and acetic acid. The aforesaid reaction can be run at a temperature from about 20°C to about 80°C for a period from about 15 minutes to about 4 hours, preferably neat conditions at about 60°C for about 2 hours.

[0160] Alternatively, compounds of formula I (g) and (h) can be prepared from compounds of formula VI according to methods described in the literature (Gauthier, J. Y.; Leblanc, Y.; Black, C.; Chan, C.-C.; Cromlish, W. A.; Gordon, R.; Kennedey, B. P.; Lau, C. K.; Léger, S.; Wang, Z.; Ethier, D.; Guay, J.; Mancini, J.; Riendeau, D.; Tagari, P.; Vickers, P.; Wong, E.; Xu, L.; Prasit, P. Bioorg. Med. Chem. Lett. 1996, 6, 87-92).

[0161] The compound of formula VII is prepared from a compound of formula VI by reaction with a reagent of the formula



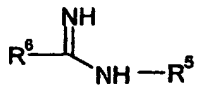
VIII

wherein L is a leaving group such as chloro, bromo, iodo or mesylate, in the presence of a base and a solvent. Suitable bases include sodium hydride (NaH) and n-butyllithium. Suitable solvents include tetrahydrofuran (THF) and dimethyl formamide (DMF). The aforesaid reaction can be conducted at a temperature from about -30°C to about the reflux temperature of the solvent, for a period of about 5 minutes to about 24 hours.

[0162] The compound of formula VI is prepared according to the methods. of Davies, I. W.; Marcoux, J.-F.; Corley, E. G.; Journet, M.; Cai, D.-W.; Palucki, M.; Wu, J.; Larsen, R. D.; Rossen, K.; Pye, P. J.; DiMichele, L.; Dormer, P.; Reider, P. J.; J. Org. Chem., Vol. 65, pp. 8415-8420 (2000). The compound of formula VIII is prepared by methods well known to those skilled in the art.

[0163] Scheme 2 refers to an alternate preparation of compounds of formula I, wherein $(R^3)_s$-phenyl-Het is (b), from compounds of the formula XIV. Compounds of the formula XIV can be prepared by the methods of Scheme 4.

[0164] Referring to Scheme 2, a compound of the formula I, wherein $(R^3)_s$-phenyl-Het is a group of the formula (b), can be prepared from a compound of the formula X by reaction with a compound of the formula



XI

wherein R^5 is hydrogen, in the presence of a polar solvent. Suitable solvents include dimethyl formamide, chloroform, DMSO, THF and ethanol, preferably dimethylformamide. The aforesaid reaction is conducted at a temperature of about 15°C to about 80°C, preferably about 60°C, for a period from about 4 hours to about 4 days, preferably 4 hours.

[0165] Alternatively, a compound of the formula I, wherein $(R^3)_s$-phenyl-Het is a group of the formula (b), can be prepared from a compound of formula XII by reaction with R^6-(C=O)H in the presence of an ammonia source. Suitable ammonia sources include ammonium trifluoroacetate, ammonia, and ammonium acetate, preferably ammonium acetate. The aforesaid reaction can be run neat or in the presence of a solvent such as alcohols (methanol, ethanol or butanol) and acetic acid. The aforesaid reaction can be run at a temperature from about 20°C to about 80°C for a period from about 15 minutes to about 4 hours, preferably neat conditions at about 60°C for about 2 hours.

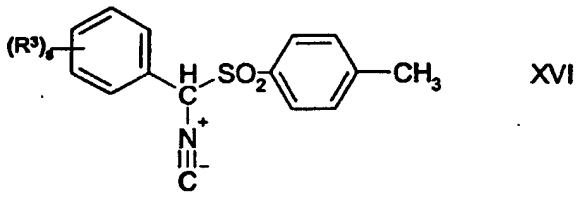
[0166] The compound of formula XII is prepared from a compound of the formula XIII by reaction with an oxidizing reagent in a polar protic solvent. Suitable oxidizing reagents include copper acetate, pyridiniumchlorochromate (PCC) and tetrapropylammonium peruthenate/N-methyl morpholine-N-oxide (TPAP/NMO), preferably cuprous acetate. Suitable solvents include acetic acid. The aforesaid reaction can be run neat or in the presence of a solvent such as alcohols (methanol, ethanol or butanol) and acetic acid. The aforesaid reaction can be run at a temperature from about 20°C to about 80°C for a period from about 15 minutes to about 4 hours, preferably neat conditions at about 60°C for about 2 hours.

[0167] Alternatively, a compound of the formula I, wherein $(R^3)_s$-phenyl-Het is a group of the formula (b), can be prepared from a compound of formula XIII, by reaction with an aldehyde of the formula R^6-(C=O)-H in the presence of cuprous acetate and an ammonia source according to methods analogous to those for the conversion of compounds of formula IV to formula I in Scheme 1.

[0168] The compound of formula XIII is prepared from a compound of the formula X by reaction with a methoxide such as described in Scheme 1 for the preparation of compounds of formula IV from compounds of formula V.

[0169] The compound of formula X is prepared from a compound of the formula XIV by reaction with Br_2 in a polar solvent. Suitable solvents include acetic acid, chloroform or methylene chloride, preferably acetic acid. The aforesaid reaction is conducted at a temperature of about 0°C to about 30°C preferably at about 22°C (room temperature) for a period from about 10 minutes to about 4 hours, preferably about 30 minutes.

[0170] Scheme 3 refers to an alternate preparation of compounds of formula I, wherein $(R^3)_s$-phenyl-Het is a group of the formula (b) or (d) and R^6 is hydrogen. Referring to Scheme 3, a compound of formula I, wherein $(R^3)_s$-phenyl-Het is of the formula (d) and R^6 is hydrogen, is prepared from a compound of formula XVII by reaction with an isocyanide of formula



XVI

in the presence of a base. Suitable bases include potassium carbonate, triethylamine, and piperazine, preferably potassium carbonate. Suitable solvents include polar solvents such as tetrahydrofuran, or N,N-dimethylformamide, preferably in N,N-dimethylformamide. The aforesaid reaction may be run at a temperature between about 22°C and about 70°C, preferably at about 22°C for a period from about 2 hours to about 4 hours, followed by about 6 hours to about 10 hours at a temperature of about 70°C.

[0171] Compounds of formula I, wherein $(R^3)_s$-phenyl-Het is of the formula (b) and R^6 is hydrogen, can be prepared in an analogous way by first preparation of the intermediate imine of formula XV by reaction of compounds of formula XVII with a suitable amine of the formula NH_2R^5 under dehydrating conditions. Such conditions include the treatment of compounds of formula XVII and an amine NH_2R^5 in a solvent such as tetrahydrofuran or dichlormethane with a dehydrating agent such as anhydrous magnesium sulfate or molecular sieves. Alternatively, the imine of formula XV

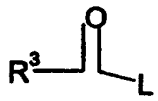
can be prepared and subsequently reacted in an aqueous media as described in the literature: (Sisko, J.; Kassik, A. J.; Mellinger, M.; Filan, J. J.; Allen, A.; Olsen, M. A.; J. Org. Chem., 65, 1516-1524 (2000)). Reactions of imines of formula XV with suitable isocynanides of formula XVI are conducted at about 22°C for a time period from about 1 day to about 21 days, preferably about 1 day.

[0172] A compound of formula XVII is prepared from a compound of formula XXIII in Sch me 4.

[0173] Scheme 4 refers to an alternate preparation of compounds of the formula I, wherein $(R^3)_s$-phenyl-Het is a group of the formula (b). Referring to Scheme 4, compounds of the formula I are prepared from compounds of the formula XVIII by reaction with an ammonia source. Suitable ammonia sources include ammonium trifluoroacetate, ammonia, and ammonium acetate, preferably ammonium trifluoroacetate. The aforesaid reaction can be run neat or in the presence of a solvent such as alcohols (methanol, ethanol or butanol) and acetic acid. The aforesaid reaction can be run at a temperature from about 60°C to about 150°C for a period from about 15 minutes to about 3 hours, preferably neat conditions at about 150°C for about 1 hour.

[0174] The compound of formula XVIII is prepared form a compound of formula XIX by reaction with an oxidizing reagent such as N-methyl morpholine N-oxide/ TPAP, Dess-Martin reagent, PCC or oxalyl chloride-DMSO , preferably N-methyl morpholine N-oxide/ TPAP. Suitable solvents for the aforesaid reaction include methylene chloride, chloroform, THF or dichloromethane. The aforesaid reaction is conducted at a temperature from about 10°C to about 30°C for a time from about 15 minutes to about 3 hours, preferably about 1 hour.

[0175] The compound of formula XIX is prepared from a compound of the formula XX by reaction with an acylating reagent of the formula,



XXI

wherein L is a leaving group, and a base. Suitable bases include triethylamine, Hunig's base, or DBU, preferably triethylamine. Suitable leaving groups include Cl, Br or activated acids. Suitable solvents for the aforesaid reaction include methylene chloride, dimethyl formamide, THF or DMF, and mixtures thereof, preferably methylene chloride. The aforesaid reaction is conducted at a temperature from about 10°C to about 30°C preferably about 22°C (room temperature) for a period from about 1 hour to about 6 hours preferably about 1 hour.

[0176] The compound of the formula XX is prepared form a compound of formula XXII by reaction with a reducing agent. Reducing agents are well known to those skilled in the art. For example, reduction of the double bond may be effected with hydrogen gas (H_2), using catalysts such as palladium on carbon (Pd/C), palladium on barium sulfate (Pd/$BaSO_4$), platinum on carbon (Pt/C), or tris(triphenylphosphine) rhodium chloride (Wilkinson's catalyst), in an appropriate solvent such as methanol, ethanol, THF, dioxane or ethyl acetate, at a pressure from about 1 to about 5 atmospheres and a temperature from about 10°C to about 60°C, as described in Catalytic Hydrogenation in Organic Synthesis, Paul Rylander, Academic Press Inc., San Diego, 31-63 (1979). The following conditions are preferred: Pd on carbon, methanol at 25°C and 50 psi of hydrogen gas pressure.

[0177] The compound of the formula XXII is prepared from a compound of formula XIV by reaction with a base or acid and an alkyl nitrite. Suitable nitrites include n-butyl nitrite, t-butyl, or iso-amyl, preferably n-butyl nitrite. Suitable bases include sodium ethoxide, sodium methoxide or potassium t-butoxide, preferably sodium ethoxide. Suitable solvents for the aforesaid reaction include alcohols (such as methanol, ethanol, propanol or butanol) or DMSO, preferably ethanol. The aforesaid reaction is conducted at a temperature of about-10°C to about 5°C preferably 0°C, for a period from about 1 hour to about 48 hours, preferably about 24 hours.

[0178] The compound of the formula XIV is prepared from a compound of the formula XXIII by reaction with a Grignard reagent of the formula $(R^3)_s$-phenyl-CH_2-M, wherein M is magnesium chloride or magnesium bromide. Suitable solvents for the aforesaid reaction are ethers (such as dimethyl ether THF, DME or dioxane), preferably THF. The aforesaid reaction is conducted at a temperature from about 0°C to about 30°C, preferably at about 22°C (room temperature), for a period from about 1 hour to about 48 hours, preferably about 6 hours.

[0179] Compounds of the formula XXIII can be made according to the methods of Scheme 6.

[0180] Scheme 5 refers to the preparation of compounds of the formula I, wherein $(R^3)_s$-phenyl-Het is a group of the formula (e). Referring to Scheme 5, a compound of the formula I can be prepared from compound of formula XXIV by reaction with a hydroxylamine (preferably a salt thereof such as the hydrochloride salt), and a base. Suitable bases include pyridine or a trialkylamine, preferably pyridine. Suitable solvents include N,N-dimethylformamide, tetrahydrofuran or pyridine, preferably pyridine. The aforesaid reaction is conducted at a temperature from about 0°C to about 100°C, preferably at about 60°C, for a period from about 1 hour to about 48 hours, preferably about 20 hours.

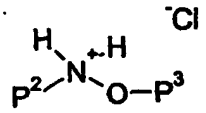
[0181] The compound of formula XXIV can be prepared from a compound of formula XXV by reaction with an ester

of the formula $(R^3)_s$-phenyl-CO_2P^1, wherein P^1 is methyl or ethyl, in the presence of a base and a solvent. Suitable bases include sodium hydride, lithium diisopropylamide, or sodium alkoxides, preferably sodium ethoxide. Suitable solvents include alcohols such as methanol, ethanol, propanol, butanol, or tetrahydrofuran, preferably ethanol. The aforesaid reaction is conducted at a temperature from about 23°C to about 65°C, preferably at about 50°C, for a period from about 2 hours to about 24 hours, preferably about 20 hours.

[0182] The compound of formula XXV can be made by methods well known to those of ordinary skill in the art and in Scheme 7 from compounds of formula XXXI by reaction with a halogenating reagant followed by reaction with a nitrile according to methods well known to those of ordinary skil in the art.

[0183] Scheme 6 refers to the preparation of compounds of the formula XVII and XXIII which are intermediates for the preparation of compounds of formula I in Schemes 3 and 4, respectfully. Referring to Scheme 6, a compound of the formula XVII is prepared from a compound of formula XXIII by reaction with a reducing agent, such as diisobutylaluminum hydride (DiBAl) in toluene, in a solvent, such as tetrahydrofuran (THF). The foresaid reaction may be run at a temperature from about -78°C to room temperature for a period from about one to about five hours.

[0184] The compound of formula XXIII is prepared from a compound of formula XXVI by reaction with a suitable activating agent and a compound of the formula,



XXVII

and a base. Suitable activating agents include thionyl chloride, EDCI and DCC, preferably oxalyl chloride. Suitable bases include triethylamine, Hunig's base, or DBU, preferably triethylamine. Suitable solvents for the aforesaid reaction include methylene chloride, dimethyl formamide, THF or DMF, and mixture thereof, preferably methylene chloride. The aforesaid reaction is conducted at a temperature from about 0°C to about 30°C preferably about 22°C (room temperature) for a period from about 6 hours to about 48 hours preferably about 12 hours.

[0185] The compound of formula XXVI is prepared from a compound of formula XXVIII by reaction with sodium nitrite under acidic conditions. Suitable acids include hydrochloric acid. The aforesaid reaction is conducted at a temperature from about 0°C to about 100°C, preferably about 22°C, for a period from about 1 hour to about 3 hours, preferably about 2 hours.

[0186] The compound of formula XXVIII is prepared from a compound of formula XXIX by reaction with a reducing agent. Reducing agents are well known to those skilled in the art. For example, reduction of the double bond may be effected with hydrogen gas (H_2), using catalysts such as palladium on carbon (Pd/C), palladium on barium sulfate (Pd/$BaSO_4$), platinum on carbon (Pt/C), or tris(triphenylphosphine) rhodium chloride (Wilkinson's catalyst), in an appropriate solvent such as methanol, ethanol, THF, dioxane or ethyl acetate, at a pressure from about 1 to about 5 atmospheres and a temperature from about 10°C to about 60°C, as described in Catalytic Hydrogenation in Organic Synthesis. Paul Rylander, Academic Press Inc., San Diego, 31-63 (1979). The following conditions are preferred: Pd on carbon, methanol at 25°C and 50 psi of hydrogen gas pressure.

[0187] The compound of formula XXIX can be prepared from a compound of formula XXX by reaction with an amine of the formula R^2NH_2. Suitable solvents include an excess of the amine reactant (neat), glyme, and toluene, preferably neat. The aforesaid reaction is conducted at a temperature from about 70°C to about 120°C, preferably 100°C, for a period from about 10 minutes to about 1 hour, preferably about 30 minutes.

[0188] The compound of the formula XXX is commercially available or can be prepared by methods well known to those skilled in the art.

[0189] Scheme 7 refers to an alternate preparation of compounds of the formula XVII which are intermediates useful in the preparation of compounds of formula I in Scheme 3. Referring to Scheme 7, a compound of the formula XVII is prepared from a compound of formula XXXI by reaction with an oxidizing reagent such as N-methyl morpholine N-oxide/ TPAP, Dess-Martin reagent, PCC or oxalyl chloride-DMSO, preferably oxalyl chloride-DMSO. Suitable solvents for the aforesaid reaction include methylene chloride, chloroform, THF or dichloromethane. The aforesaid reaction is conducted at a temperature from about -78°C to about 22°C for a time from about 15 minutes to about 3 hours, preferably about 1 hour.

[0190] The compound of the formula XXXI is prepared from a compound of the formula XXXII by reaction with a reducing reagant. Suitable reducing agents include lithium borohydride, sodium borohydride ($NaBH_4$), sodium cyanoborohydride ($NaCNBH_3$), lithium aluminum hydride ($LiAlH_4$) and borane in THF (BH_3·THF). Suitable solvents include methanol, ethanol, THF, diethyl ether, dioxane and tetrahydrofuran. The aforesaid reaction is conducted at a temperature from about 0°C to about 70°C, preferably 65°C, for a period from about 10 minutes to about 1 hour, preferably about 30 minutes.

[0191] The compound of formula XXXII is prepared from a compound of formula XXXIII by reaction with an alkylating reagant of the formula R^2L', wherein L' is halo or other leaving group such as mesyl, in the presence of a base and a solvent. Suitable bases include sodium hydride and cesium carbonate. Suitable solvents include dimethyl sulfoxide, NN-dimethylformamide. The aforesaid reaction is conducted at a temperatur from about 0°C to about 30°C, preferably about 22°C, for a period from about 10 minutes to about 2 hours, preferably about 1 hour.

[0192] Compounds of the formula XXXIII are commercially available or can be made by methods well known to those of ordinary skill in the art

[0193] Scheme 8 refers to an alternate preparation of compounds of the formula XXVI, wherein R^2 is optionally substituted (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, and (C_1-C_{10})heterocyclic; which are intermediates in Scheme 6 useful in the preparation of compounds of formula I, wherein R^2 is optionally substituted (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, and (C_1-C_{10})heterocyclic. Referring to Scheme 8, a compoound of formula XXVI is prepared from a compound of formula XXVIII by reaction with sodium nitrite under acidic conditions. Suitable acids include hydrochloric acid. The aforesaid reaction is conducted at a temperature from about 0°C to about 100°C, preferably about 22°C, for a period from about 1 hour to about 3 hours, preferably about 2 hours.

[0194] The compound of formula XXVIII, wherein R^2 is optionally substituted (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, or (C_1-C_{10})heterocyclic; is prepared from a compound of formula XXXI by reductive alkylation with a compound of the formula $R^1(C=O)R^1$, wherein each R^1 is independently selected. One of ordinary skill in the art will understand that $R^1(C=O)R^1$ is the precursor to R^2 which is formed by reduction in the presence of a reducing agent and a solvent. Suitable reducing agents include sodium borohydride, sodium cyanoborohydride and sodium triacetoxyborohydride, preferably triacetoxyborohydride. Suitable solvents include acetic acid, THF, DMF and dimethylsulfoxide, prefereably a mixture of acetic acid, THF and DMF. The aforesaid reaction is conducted at a temperature from about 0°C to about 30°C, preferably about 22°C, for a period from about 10 minutes to about 2 hours, preferably about 1 hour.

[0195] The compound of formula XXXI is commercailly available or can be made by methods well known to those of ordinary skill in the art.

[0196] The compounds of the formula I which are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent, and subsequently convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is obtained.

[0197] The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as chloride, bromide, iodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

[0198] Those compounds of the formula I which are also acidic in nature, e.g., where R^2, R^3, R^4, R^5, R^6, or R^7 includes a COOH or tetrazole moiety, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the herein described acidic compounds of formula I. These non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum product yields.

[0199] The activity of the compounds of the invention for the various disorders described above can be determined according to one or more of the following assays. All of the compounds of the invention, that were tested, had an IC_{50} of less than 10 μM in the TNFα and MAPKAP *in vitro* assays or an ED_{50} of less than 50 mg/kg in the *in vivo* TNFα assay.

[0200] The compounds of the present invention also possess differential activity (i.e. are selective for) for one or more p38 kinases (i.e. α, β, χ and δ). Certain compounds are selective for p38α over p38β, χ and δ, other compounds are selective for p38β over p38α, χ and δ, other compounds are selective for p38 α and β over p38 χ and δ. Selectivity is measured in standard assays as an IC_{50} ratio of inhibition in each assay.

INHIBITION OF TNF-ALPHA PRODUCTION BY HUMAN LPS-TREATED MONOCYTES

[0201] Mononuclear cells are isolated from heparinized blood (1.5 ml of 1000 units / ml heparin for injection, Elkins-Sinn,Inc. added to ach 50 ml sample) using Accuspin System-Histopaque-1077 tubes® (Sigma A- 7054). Thirty-five milliliters of whole blood are added to each tube and the tubes are centrifuged at 2100 rpm for 20 minutes in a Beckman GS-6KR centrifuge with the brake off at room temperature. The mononuclear cells which collect at the interface are removed, diluted with Macrophage serum free medium (Gibco-BRL) (Medium) to achieve a final volume of 50 ml, and collected by centrifugation for 10 minutes. The supernatant is discarded and the cell pellet is washed 2 times with 50 ml of Medium. A sample of the suspended cells is taken before the second wash for counting. Based on this count, the washed cells are diluted with Medium containing 1% FBS to a final concentration of 2.7×10^6 cells / ml and 75 µl of the cell suspension is added to each well of a 96 well plate.

Compound Preparation:

[0202] Compounds are routinely tested at final concentrations from 2 µM to 0.016 µM, but may be tested at other concentrations, depending on activity. Test agents are diluted with DMSO to a final concentration of 2mM. From this stock solution, compounds are first diluted 1:25 (5 µl of 2 mM stock + 120 µl Medium containing 400 ng/ml LPS and 1% FBS then 40 µl of this dilution is diluted with 360 µl of Medium with LPS. Serial dilutions (1/5) are performed by transferring 20 µl of this dilution to 80 µl of Medium containing both LPS and 0.4% DMSO, resulting in solutions containing 8 µM, 1.6 µM, 0.32 µM and 0.064 µM of test agent.

Assay:

[0203] The assay is initiated by adding 25 µl of the diluted compounds to the mononuclear cell suspension and incubating the cells at 37 C and 5% CO_2 for 4 hours.

[0204] The 96-well plates are then centrifuged for 10 minutes at 2000 rpm at 4°C in a Beckman GS-6KR centrifuge to remove cells and cell debris. A 90 µl aliquot of each supernatant is removed and transferred to a 96 well round bottom plate, and this plate is centrifuged a second time to insure that all cell debris is removed. 80 µl of the supernatant is removed and transferred to a new round bottom plate.

[0205] Supernatants are analyzed for TNF-α content using R&D ELISA. 25 µl of each sample is added to an ELISA well containing 25 µl of assay diluent RD1F and 75 µl of assay diluent RD5. The assay is run following kit directions except 100 µl of conjugate and substrate solutions are used.

INTERPRETATION

[0206] The amount of TNF-α immunoreactivity in the samples is calculated as follows:

$$\% \text{ Control} = (X-B) / (TOT-B) \times 100$$

where

X = OD_{450} nm of the test compound well
B = OD_{450} of Reagent Blank wells on the ELISA
Total = OD_{450} of cells that were treated with 0.1% DMSO only.

MAPKAP KINASE-2 ASSAY

Monocyte preparation.

[0207] Mononuclear cells are collected from heparinized human blood as detailed above. The washed cells are seeded into 6-well cluster plates at a density of 1×10^7 cells/well (in 2 ml of Medium). The plates are incubated at 37°C in a 5% CO_2 environment for 2 hours to allow adherence of the monocytes, after which time media supernatants containing non-adherent cells are removed by aspiration and 2 ml of fresh medium are added to each well. Plates are incubated overnight at 37°C in a 5% CO_2 environment.

C II Activation:

[0208] Media are removed by aspiration. The attached cells are rinsed twice with fresh Medium, then 2 ml of D-MEM medium containing 10% heat inactivated FBS are added to each well. Test compounds are prepared as 30 mM stock solutions in DMSO and diluted to 1250, 250, 50, 10, 2, and 0.4 μM in D-MEM containing 1% DMSO and 10% FBS. To individual wells of the monocyte cultures, 20 μl of these test agent dilutions are added resulting in final test agent concentrations of 12.5, 2.5, 0.5, 0.1, 0.02 and 0.004 μM. After a 10 minute preincubation period, 20 μl of a 10 μg/ml LPS solution are added to each well and the plates are incubated at 37°C for 30 min. Media subsequently are removed by aspiration, the attached monocytes are rinsed twice with phosphate buffered saline, then 1 ml of phosphate buffered saline containing 1% Triton X-100 (Lysis Buffer; also containing 1 Complete™ tablet [Boehringer #1697498] per 10 ml of buffer) is added to each well. The plates are incubated on ice for 10 minutes, after which the lysates are harvested and transferred to centrifugation tubes. After all samples are harvested, they are clarified by centrifugation (45,000 rpm for 20 min) and the supernatants recovered.

MAPKAP Kinase-2 Immunoprecipitation:

[0209] 5 μl of anti-MAPKAP kinase-2 antiserum (Upstate Biotechnology #06-534) is added to a microcentrifuge tube (1 tube for each of the above cell lysates) containing 1 ml of a 5% suspension of Protein G-Sepharose (Sigma #P3296) in PBS. These mixtures are incubated for 1 hour at 4°C (with rocking) after which the beads, containing bound IgG, are recovered by centrifugation and washed twice with 1 ml of 50 mM Tris, pH 7.5, 1 mM EDTA, 1 mM EGTA, 0.5 mM orthovanadate, 0.1% 2-mercaptoethanol, 1% Triton X-100, 5 mM sodium pyrophosphate, 10 mM sodium β-glycerophosphate, 0.1 mM phenymethylsulfonyl fluoride, 1 μg/ml leupeptin, 1 μg/ml pepstatin, and 50 mM sodium fluoride (Buffer A) by repeated centrifugation. An individual monocyte cell extract (prepared above) is then transferred to each tube containing a pellet of IgG-coated Protein G-Sepharose, and these mixtures are incubated for 2 hours at 4°C (with rocking). The beads subsequently are harvested by centrifugation, and the resulting bead pellets are washed once with 0.5 ml of Buffer A containing 0.5 M NaCl, once with 0.5 ml of Buffer A, and once with 0.1 ml of a buffer composed of 20 mM MOPS, pH 7.2, 25 mM sodium β-glycerophosphate 5 mM EGTA, 1 mM orthovanadate, and 1 mM dithiothreitol (Buffer B).

MAPKAP Kinase-2 Activity Assessment.

[0210] A kinase reaction mixture stock is prepared as follows: 2.2 μl of 10 mCi/ml γ[^{32}P]ATP, 88 μl of 1.3 μg/ml solution of MAPKAP Kinase-2 substrate peptide (Upstate Biotechnology #12-240), 11 μl of 10 mM ATP, 8.8 μl of 1 M $MgCl_2$, and 770 μl of Buffer B. To each of the immune complex-Protein G-pellets, 40 μl of the kinase reaction mixture are added and the tubes are incubated for 30 minutes at 30°C. The tubes then are clarified by centrifugation and 25 μl of each supernatant is spotted onto a P81 filter paper disk (Whatman #3698-023). After allowing all fluid to soak into the filter, each disk is placed into an individual well of 6-well cluster plates and the filters are washed sequentially with 2 ml of 0.75% phosphoric acid (3 washes/15 min each) and once with acetone (10 min). The filters then are air dried and transferred to liquid scintillation vials containing 5 ml of scintillation fluid. Radioactivity is determined in a liquid scintillation counter. The amount of radioactivity bound to the filter at each test agent concentration is expressed as a percentage of that observed from cells stimulated with LPS in the absence of a test agent.

IN VIVO INHIBITION OF TNFα

[0211] Rats were weighed and dosed with vehicle (0.5% methyl cellulose, Sigma) or drug. One hour later, animals were injected i.p. with LPS (50 ug/rat, Sigma L-4130). Ninety minutes later, animals were sacrificed by asphyxiation with CO_2 and bled by cardiac puncture. Blood was collected in Vaccutainer tubes and spun for 20 minutes at 3000 rpm. Serum was assayed for TNFα levels using an ELISA (R&D Systems).

[0212] The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention may be formulated for oral, buccal, intranasal, parenteral (e.g., intravenous, intramuscular or subcutaneous), topical or rectal administration or in a form suitable for administration by inhalation or insufflation.

[0213] For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions,

syrups or susp nsions, or they may be presented as a dry product for constitution with water or oth r suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters or thyl alcohol); and preservatives (.g., methyl or propyl p-hydroxybenzoates or sorbic acid).

[0214] For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner.

[0215] The compounds of formula I can also be formulated for sustained delivery according to methods well known to those of ordinary skill in the art. Examples of such formulations can be found in United States Patents 3,538,214, 4,060,598, 4,173,626, 3,119,742, and 3,492,397, which are herein incorporated by reference in their entirety.

[0216] The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[0217] The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

[0218] For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

[0219] A proposed dose of the active compounds of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above (inflammation) is 0.1 to 200 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

[0220] Aerosol formulations for treatment of the conditions referred to above in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains 20μg to 1000μg of the compound of the invention. The overall daily dose with an aerosol will be within the range 100μg to 10 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

[0221] Aerosol combination formulations for treatment of the conditions referred to above (e.g., adult respiratory distress syndrome) in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains from about 1 μg to 1000 μg of the compound of the invention. The overall daily dose with an aerosol will be within the range 100 μg to 10 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

[0222] Aerosol formulations for treatment of the conditions referred to above (e.g., adult respiratory distress syndrome) in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains from about 20 μg to 1000 μg of the compound of the invention. The overall daily dose with an aerosol will be within the range 100 μg to 10 mg of the p38 kinase inhibitor. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

[0223] This invention also encompasses pharmaceutical compositions containing and methods of treating or preventing comprising administering prodrugs of compounds of the formula I. Compounds of formula I having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues which are covalently joined through peptide bonds to free amino, hydroxy or carboxylic acid groups of compounds of formula I. The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline homocysteine, homoserine, ornithine and methionine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters which are covalently bonded to the above substituents of formula I through the carbonyl carbon prodrug sidechain.

[0224] The following Examples illustrate the preparation of the compounds of the present invention. Melting points are uncorrected. NMR data are reported in parts per million (d) and are referenced to the deuterium lock signal from the sample solvent (deuteriochloroform unless otherwise specified). Mass Spectral data wer obtained using a Micromass ZMD APCI Mass Spectrometer equipped with a Gilson gradient high performance liquid chromatograph. The following solvents and gradients were used for the analysis. Solvent A; 98% water/2% acetonirile/0.01% formic acid

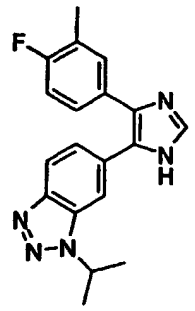
and solvent B; acetonitrile containing 0.005% formic acid. Typically, a gradient was run over a period of about 4 minutes starting at 95% solvent A and ending with 100% solvent B. The mass spectrum of the major eluting component was then obtained in positive or negative ion mode scanning a molecular weight range from 165 AMU to 1100 AMU. Specific rotations were measured at room temperature using the sodium D line (589 nm). Commercial reagents were utilized without further purification. THF refers to tetrahydrofuran. DMF refers to N,N-dimethylformamide. Chromatography refers to column chromatography performed using 32-63 mm silica gel and executed under nitrogen pressure (flash chromatography) conditions. Room or ambient temperature refers to 20-25°C. All non-aqueous reactions were run under a nitrogen atmosphere for convenience and to maximize yields. Concentration at reduced pressure means that a rotary evaporator was used.

[0225] One of ordinary skill in the art will appreciate that in some cases protecting groups may be required during preparation. After the target molecule is made, the protecting group can be removed by methods well known to those of ordinary skill in the art, such as described in Greene and Wuts, "Protective Groups in Organic Synthesis" (2nd Ed, John Wiley & Sons 1991).

EXAMPLE 1

6-[5-(4-FLUORO-3-METHYL-PHENYL)-3H-IMIDAZOL-4-YL]-1-ISOPROPYL-1H-BENZOTRIAZOLE

[0226]

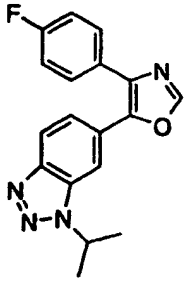


[0227] To a stirred solution of 3-isopropyl-3H-benzotriazole-5-carbaldehyde (150 mg) in 15 mL of THF was added 0.16 mL of concentrated ammonium hydroxide. The flask was sealed with a plastic cap and stirred overnight. Piperazine (75 mg) was added, followed by 4-fluoro-3-methylphenyl-toylsulfonomethylisocyanide (312 mg), and the mixture was stirred overnight. The mixture was filtered and the filtrate was concentrated and purified by flash chromatography (eluting with 4:1 ethyl acetate/hexanes to give 130 mg of the title compoound. MASS SPECTRUM 336 M+1.

EXAMPLE 2

6-[4-(4-FLUORO-PHENYL)-OXAZOL-5-YL]-1-ISOPROPYL-1H-BENZOTRIAZOLE

[0228]



[0229] A solution of 3-isopropyl-3H-benzotriazole-5-carbaldehyde (60 mg), potassium carbonate (49 mg), and

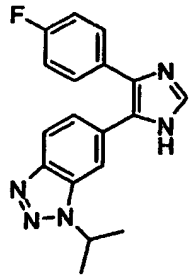
4-fluorophenyl-toylsulfonomethylisocyanide (101 mg) in 7.5 mL of dimethyl formamide was stirred overnight. The reaction mixture was concentrated to 1 mL of volume and heated at 75°C for 2 hours. The mixture was cooled to 22°C, diluted with water, and extracted with ethyl acetate. The extract was washed with water, dried (sodium sulfate), filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (eluting with 2:3 ethyl acetate/hexanes) to give 80 mg of 6-[4-(4-fluoro-phenyl)-oxazol-5-yl]-1-isopropyl-1H-benzotriazole; MASS SPECTRUM 323 (M+1).

[0230] The following compounds were made in an analogous fashion to the methods described in Examples 1 or 2.

EXAMPLE 3

6-[5-(4-FLUORO-PHENYL)-3H-IMIDAZOL-4-YL]-1-ISOPROPYL-1H-BENZOTRIAZOLE

[0231]

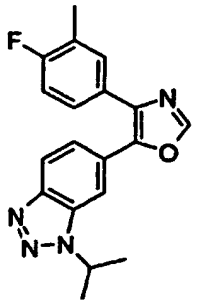


MASS SPECTRUM 322 (M+1).

EXAMPLE 4

6-[4-(4-FLUORO-3-METHYL-PHENYL)-OXAZOL-5-YL]-1-ISOPROPYL-1H-BENZOTRIAZOLE

[0232]



MASS SPECTRUM 337 (M+1).

EXAMPLE 5

6-[5-(4-FLUORO-PHENYL)-3H-IMIDAZOL-4-YL]-1-METHYL-1H-BENZOTRIAZOLE

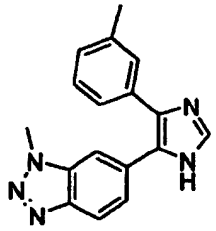
[0233]

MASS SPECTRUM 294 (M+1).

EXAMPLE 6

1-METHYL-6-(5-M-TOLYL-3H-IMIDAZOL-4-YL)-1H-BENZOTRIAZOLE

[0234]

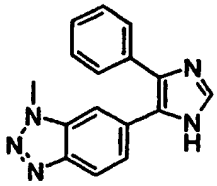


MASS SPECTRUM 290 (M+1).

EXAMPLE 7

1-METHYL-6-(5-PHENYL-3H-IMIDAZOL-4-YL)-1H-BENZOTRIAZOLE

[0235]

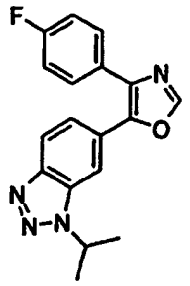


MASS SPECTRUM 276 (M+1).

EXAMPLE 8

6-[4-(4-FLUORO-PHENYL)-OXAZOL-5-YL]-1-ISOPROPYL-1H-BENZOTRIAZOLE

[0236]

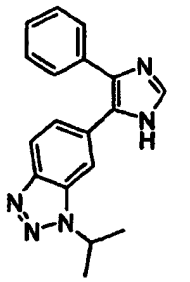


MASS SPECTRUM 323 (M+1).

EXAMPLE 9

1-ISOPROPYL-6-(5-PHENYL-3H-IMIDAZOL-4-YL)-1H-BENZOTRIAZOLE

[0237]

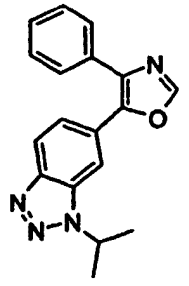


MASS SPECTRUM 304 (M+1).

EXAMPLE 10

1-ISOPROPYL-6-(4-PHENYL-OXAZOL-5-YL)-1H-BENZOTRIAZOLE

[0238]

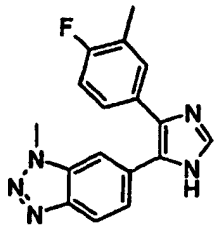


MASS SPECTRUM 305 (M+1).

EXAMPLE 11

6-[5-(4-FLUORO-3-METHYL-PHENYL)-3H-IMIDAZOL-4-YL]-1-METHYL-1H-BENZOTRIAZOLE

[0239]

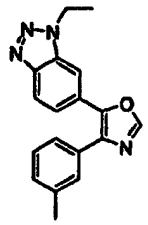


MASS SPECTRUM 308 (M+1).

EXAMPLE 12

1-ETHYL-6-(4-M-TOLYL-OXAZOL-5-YL)-1H-BENZOTRIAZOLE

[0240]

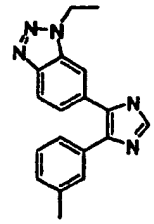


MASS SPECTRUM 305(M+1).

EXAMPLE 13

1-ETHYL-6-(5-M-TOLYL-3H-IMIDAZOL-4-YL)-1H-BENZOTRIAZOLE

[0241]

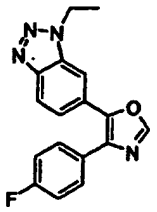


MASS SPECTRUM 304 (M+1).

EXAMPLE 14

1-ETHYL-6-[4-(4-FLUORO-PHENYL)-OXAZOL-5-YL]-1H-BENZOTRIAZOLE

[0242]

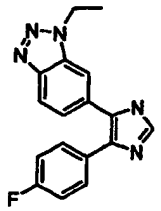


MASS SPECTRUM 309 (M+1).

EXAMPLE 15

1-ETHYL-6-[5-(4-FLUORO-PHENYL)-3H-IMIDAZOL-4-YL]-1H-BENZOTRIAZOLE

[0243]

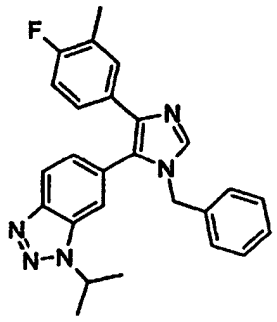


MASS SPECTRUM 308 (M+1).

EXAMPLE 16

6-[3-BENZYL-5-(4-FLUORO-3-METHYL-PHENYL)-3H-IMIDAZOL-4-YL]-1-ISOPROPYL-1H-BENZOTRIAZOLE

[0244]

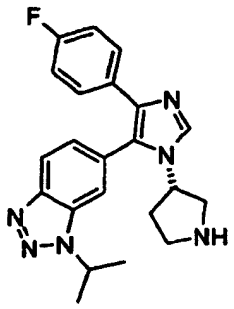


MASS SPECTRUM 426 (M+1).

EXAMPLE 17

6-[5-(4-FLUORO-PHENYL)-3S-PYRROLIDIN-3-YL-3H-IMIDAZOL-4-YL]-1-ISOPROPYL-1H-BENZOTRIAZOLE MONO CITRATE SALT

[0245]

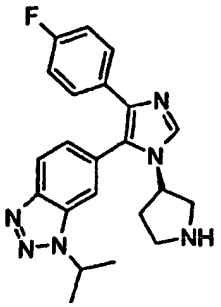


MASS SPECTRUM 391 (M+1).

EXAMPLE 18

6-[5-(4-FLUORO-PHENYL)-3R-PYRROLIDIN-3-YL-3H-IMIDAZOL-4-YL]-1-ISOPROPYL-1H-BENZOTRIAZOLE

[0246]

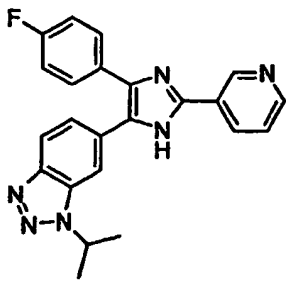


MASS SPECTRUM 391 (M+1).

EXAMPLE 19

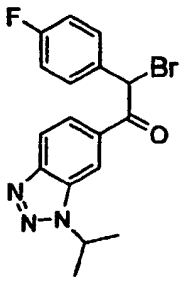
6-[5-(4-FLUORO-PHENYL)-2-PYRIDIN-3-YL-3H-IMIDAZOL-4-YL]-1-ISOPROPYL-1H-BENZOTRIAZOLE

[0247]



Step (A) 2-(4-Fluoro-phenyl)-1-(3-isopropyl-3H-benzotriazol-5-yl)-ethanone

[0248] To a stirred, cold (-10 °C) mixture of 519 mg 3-isopropyl-3H-benzotriazole-5-carboxylic acid methoxy-methyl-amide in 2 mL of tetrahydrofuran was added 17 mL of 4-fluorophenylmagnesium bromide (0.25 M in diethyl ether). The resulting suspension was stirred for 1 hour before the mixture was concentrated to near dryness. The residue was taken-up into 20 mL of tetrahydrofuran and 6 mL more 4-fluorophenylmagnesium bromide (0.25 M in diethyl ether) was added. The resulting solution was stirred for 15 minutes before it was diluted with water and the pH of the mixture was adjusted to 7 using 1 M hydrochloric acid. The mixture was extracted with ethyl acetate (3x), and the combined extracts were washed with brine, dried (sodium sulfate), filtered, and the filtrate was concentrated to give about 1 g of a yellow oil. This oil was purified by flash chromatography (eluting with 3:1 hexanes/ethyl acetate) to give 467 mg of 2-(4-fluoro-phenyl)-1-(3-isopropyl-3H-benzotriazol-5-yl)-ethanone as a clear oil.



Step (B) 2-Bromo-2-(4-fluoro-phenyl)-1-(3-isopropyl-3H-benzotriazol-5-yl)-ethanone

[0249] To a stirred solution of 191 mg of 2-(4-fluoro-phenyl)-1-(3-isopropyl-3H-benzotriazol-5-yl)-ethanone in 2 mL of acetic acid was added 0.64 mL of bromine (1 M in acetic acid). The mixture was heated at 50 °C for 3 hours. The reaction mixture was cooled to 22 °C and concentrated to dryness. The residue was taken-up into ethyl acetate and washed with saturated aqueous sodium bicarbonate, brine; the organic layer was dried (sodium sulfate), filtered and the filtrate was concentrated to give 222 mg of 2-bromo-2-(4-fluoro-phenyl)-1-(3-isopropyl-3H-benzotriazol-5-yl)-ethanone as a light yellow oil. This material was used without further purification.

Step (C) 6-[5-(4-Fluoro-phenyl)-2-pyridin-3-yl-3H-imidazol-4-yl]-1-isopropyl-1H-benzotriazole

[0250] To a stirred solution of 29 mg of 2-bromo-2-(4-fluoro-phenyl)-1-(3-isopropyl-3H-benzotriazol-5-yl)-ethanone in 0.38 mL of N,N-dimethylformamide was added 75 mg of cesium carbonate and 24 mg of 3-amidinopyridine hydrochloride. The mixture was heated at 50 °C for 30 min. The orange-brown mixture was cooled to 22 °C, transferred to

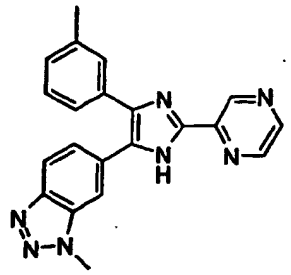
a separatory funnel with water, and extracted with ethyl acetate (3x). The combined organic layers were washed with brine, dried (sodium sulfate), filtered, and the filtrate was concentrated to an orange oil. This oil was purified by flash chromatography (eluting with ethyl acetate) to give 12 mg of 6-[5-(4-fluoro-ph nyl)-2-pyridin-3-yl-3H-imidazol-4-yl]-1-isopropyl-1H-benzotriazole as a white solid. LCMS m/z 399 (M+1).

[0251] The following Examples were prepared acording to the methods analogous to those of Example 19.

EXAMPLE 20

1-METHYL-6-(2-PYRAZIN-2-YL-5-M-TOLYL-3H-IMIDAZOL-4-YL)-1H-BENZOTRIAZOLE

[0252]

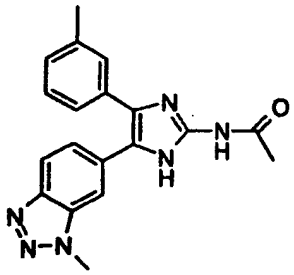


MASS SPECTRUM 368 (M+1).

EXAMPLE 21

N-[5-(3-METHYL-3H-BENZOTRIAZOL-5-YL)-4-M-TOLYL-1H-IMIDAZOL-2-YL]-ACETAMIDE

[0253]

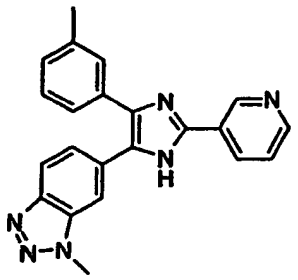


MASS SPECTRUM 347 (M+1).

EXAMPLE 22

1-METHYL-6-(2-PYRIDIN-3-YL-5-M-TOLYL-3H-IMIDAZOL-4-YL)-1H-BENZOTRIAZOLE

[0254]

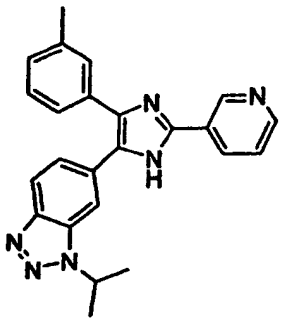


MASS SPECTRUM 367(M+1).

EXAMPLE 23

1-ISOPROPYL-6-(2-PYRIDIN-3-YL-5-M-TOLYL-3H-IMIDAZOL-4-YL)-1H-BENZOTRIAZOLE

[0255]

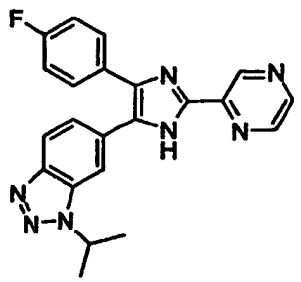


MASS SPECTRUM 395 (M+1).

EXAMPLE 24

6-[5-(4-FLUORO-PHENYL)-2-PYRAZIN-2-YL-3H-IMIDAZOL-4-YL]-1-ISOPROPYL-1H-BENZOTRIAZOLE

[0256]



MASS SPECTRUM 400 (M+1).

PREPARATION 1

1-METHYL-1H-BENZOTRIAZOLE-5-CARBALDEHYDE

3-Methyl-3H-benzotriazole-5-carboxylic acid methyl ester

[0257] To a stirred, cold (0°C) solution of 1,2,3-benzotriazole-5-carboxylic acid methyl ester (2.51 g) in dimethylformamide was added 60% sodium hydride (370 mg) portion wise. After 20 minutes, methyl iodide (0.87 mL) was added. The reaction was quenched by the addition of water after 30 minutes. The mixture was extracted with ethyl acetate; the extracts were washed with water, and brine, and dried (sodium sulfate). Filtration and concentration of the filtrate gave a residue from which 716 mg of 1-methyl-1H-benzotriazole-5-carboxylic acid methyl ester crystallized (hot ethyl acetate). The mother liquor was purified by flash chromatography (eluting with 3:2 hexanes/ethyl acetate) to give 890 mg of 2-methyl-2H-benzotriazole-5-carboxylic acid methyl ester and 490 mg of 3-methyl-3H-benzotriazole-5-carboxylic acid methyl ester. Structural assignments were made on the basis of proton NMR and nOe experiments.

1-Methyl-1H-benzotriazole-5-carbaldehyde

[0258] 3-Methyl-3H-benzotriazole-5-carboxylic acid methyl ester was taken on separately to the corresponding aldehydes by reduction with lithium aluminum hydride (1 equivalent) in anhydrous dimethoxyethane. The resulting alcohols were oxidized using 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (1 equivalent), tetrabutylammonium chloride (1 equivalent), and N-chlorosuccinimide (1.3 equivalent) in methylene chloride and pH 8.6 sodium bicarbonate/potassium carbonate buffer to give 3-methyl-3H-benzotriazole-5-carbaldehyde.

PREPARATION 2

3-ISOPROPYL-3H-BENZOTRIAZOLE-5-CARBALDEHYDE

3-Isopropyl-3H-benzotriazole-5-carboxylic acid

[0259] To a stirred mixture of 3,4-diaminobenzoic acid (15.2 g), in 200 mL of tetrahydrofuran, 30 mL of dimethyl formamide, 7.3 mL of acetone, and 5.7 mL of acetic acid, was added 31.8 g of sodium triacetoxyborohydride in portions. After 3 hours the mixture was filtered through diatomaceous earth and washed with tetrahydrofuran. The filtrate was concentrated to dryness. Crystallization of the residue with ethyl acetate/hexanes gave 11 grams of 4-amino-3-isopropylamino-benzoic acid.

[0260] To a stirred, cold (0 °C) mixture of 4-amino-3-isopropylamino-benzoic acid (11 g) in 120 mL of 6 N hydrochloric acid was added drop-wise a solution of 5.9 g of sodium nitrite in 40 mL of water. After 2 hours the solids were collected by filtration, washed with water, and dried to give 9 grams of 3-isopropyl-3H-benzotriazole-5-carboxylic acid.

3-isopropyl-3H-benzotriazole-5-carboxylic acid methoxy-methyl-amide

[0261] To a stirred mixture of 3-isopropyl-3H-benzotriazole-5-carboxylic acid (9 g) in 150 mL of methylene chloride and 0.15 mL of DMF was added 5.0 mL of oxalyl chloride. The solution was stirred overnight before 27 mL of N,N-diisopropylamine and 5.6 g of N,O-dimethylhydroxylamine hydrochloride was added. The mixture was stirred for 3 days before mixture was washed with a solution of sodium dihydrogenphosphate, aqueous bicarbonate, dilute hydrochloric acid, brine, dried (sodium sulfate), filtered, and the filtrate was concentrated to a dark oil. This oil was purified by flash chromatography (eluting with 3:2 ethyl acetate/hexanes) to afford 10.4 g of 3-isopropyl-3H-benzotriazole-5-carboxylic acid methoxy-methyl-amide as brown oil.

3-isopropyl-3H-benzotriazole-5-carbaldehyde

[0262] To a stirred, cold (-78°C) solution of 3-isopropyl-3H-benzotriazole-5-carboxylic acid methoxy-methyl-amide (4.26g) in 20 mL of toluene was added drop-wise 17.2 mL of DIBAL in toluene (1 M). The mixture was stirred for 1 hour at -78°C before warming to 0°C. The reaction was quenched with aqueous 1 N hydrochloric acid, diluted with water and extracted with ethyl acetate (3 times). The combined extracts were washed with water, brine, dried (sodium sulfate), filtered, and the filtrate was concentrated to give a yellow oil. This oil was purified by flash chromatography (eluting with 2:1 hexanes/ethyl acetate) to give 2.24 g of 3-isopropyl-3H-benzotriazole-5-carbaldehyde as a yellow oil which crystallized upon standing; MS 190 M+1.

PREPARATION 3

3-ETHYL-3H-BENZOTRIAZOLE-5-CARBALDEHYDE

3-Chloro-4-nitro-benzonitrile

[0263] Sodium nitrite (6.78 g in water (40 mL) at 0°C) was slowly added to a solution of 4-amino-3-chloro-benzonitrile (10.5 g) in water (30 mL) and concentrated hydrochloric acid (30 mL) also at 0°C. After 10 minutes the solution was poured onto a suspension of cuprous oxide (3.48 g) and sodium nitrite (31.69 g) in water (100 mL) at 0°C. The ensuing mixture was stirred at 0°C for 1 hour then at 23°C for 1 hour. The resulting mixture was extracted with dichloromethane and the organic layer washed with saturated sodium chloride. The separated organic layer was dried over sodium sulfate and then concentrated to give 3-chloro-4-nitro-benzonitrile (11.31 g).

3-Ethylamino-4-nitro-benzonitrile

[0264] Monoethylamine was bubbled though a solution of 3-chloro-4-nitro-benzonitrile (0.49 g) in tetrahydrofuran (1 mL). The reaction vial was sealed and allowed to stand for 18 hours at 23°C. The resulting mixture was diluted with ethyl acetate and saturated sodium bicarbonate and extracted. The organic layer was dried with sodium sulfate and concentrated. Silica gel chromatography using 5% ethyl acetate in hexanes as eluent gave 3-ethylamino-4-nitro-benzonitrile (0.3 g).

4-Amino-3-ethylamino-benzonitrile

[0265] 3-Ethylamino-4-nitro-benzonitrile (0.3g) was diluted with ethanol (5 mL) and was treated with 10% palladium on carbon (Pd/C)(0.070g). The mixture was then shaken in a hydrogenation shaker under an atmosphere of hydrogen (40 psi) for 30 minutes. The resulting mixture was filtered through diatomaceous earth and concentrated. Silica gel chromatography using 20% ethyl acetate in hexanes as eluent gave 4-amino-3-ethylamino-benzonitrile (0.08 g).

3-Ethyl-3H-benzotriazole-5-carbonitrile

[0266] 3-Ethyl-3H-benzotriazole-5-carbonitrile was prepared using the procedures previously described for the synthesis of 3-isopropyl-3H-benzotriazole-5-carboxylic acid ethyl ester.

3-Ethyl-3H-benzotriazole-5-carboxylic acid

[0267] 3-Ethyl-3H-benzotriazole-5-carbonitrile (0.065g) was diluted with lithium hydroxide (2 M in water) then heated to 100°C for 2 hours. The mixture was then cooled to 23 C, acidified with 1 N hydrochloric acid and extracted with ethyl acetate. The organic layer was dried with sodium sulfate and concentrated to give 3-ethyl-3H-benzotriazole-5-carbox-

ylic acid (0.059 g).

3-Ethyl-3H-benzotriazole-5-carboxylic acid methyl ester

[0268] 3-Ethyl-3H-benzotriazole-5-carboxylic acid (0.15 g) was diluted with methanol and treated with HCl (gas). The reaction was then heated to 65°C for 18 hours. The mixture was allowed to cool to 23°C and was diluted with saturated sodium bicarbonate and extracted with ethyl acetate. The organic layer was dried with sodium sulfate and concentrated to give 3-ethyl-3H-benzotriazole-5-carboxylic acid methyl ester (0.143 g).

(3-Ethyl-3H-benzotriazol-5-yl)-methanol

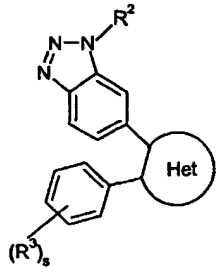
[0269] 3-Ethyl-3H-benzotriazole-5-carboxylic acid methyl ester (0.143 g) was diluted with tetrahydrofuran (2 mL) and methanol (0.06 mL). Lithium borohydride (0.023 g) was added and the solution was allowed to stand at 23°C for 30 minutes. The reaction was then poured onto saturated ammonium chloride and extracted with ethyl acetate. The organic layer was dried with sodium sulfate and concentrated to give (3-Ethyl-3H-benzotriazol-5-yl)-methanol (0.13 g).

3-Ethyl-3H-benzotriazole-5-carbaldehyde

[0270] 3-Ethyl-3H-benzotriazole-5-carbaldehyde was prepared from (3-Ethyl-3H-benzotriazol-5-yl)-methanol by a Swern oxidation.

Claims

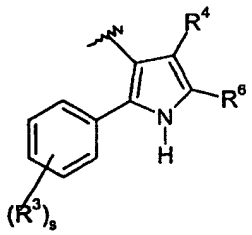
1. A compound of the formula



I

or a pharmaceutically acceptable salt or solvate thereof,
wherein

Het is an optionally substituted 5-membered heteroaryl which taken together with $(R^3)_s$ phenyl is selected from the group consisting of



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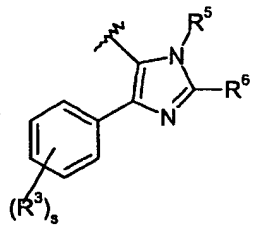
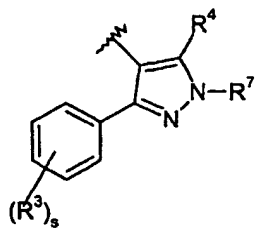
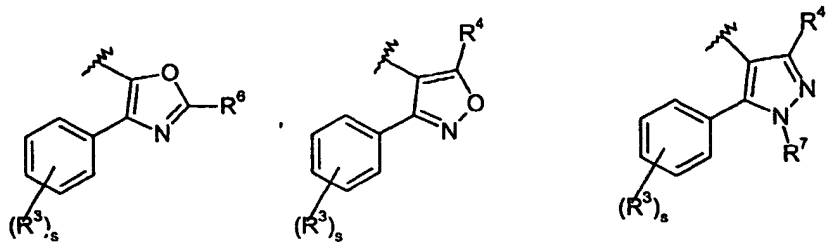


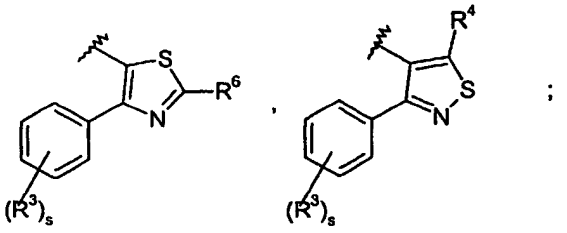
(b)



(c)



(d) (e) (f)



(g) (h)

R^2 is selected from the group consisting of hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, phenyl, $(C_1\text{-}C_{10})$heteroaryl and $(C_1\text{-}C_{10})$heterocyclic; wherein each of the aforesaid $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, phenyl, $(C_1\text{-}C_{10})$heteroaryl and $(C_1\text{-}C_{10})$heterocyclic substituents may optionally be independently substituted by one to four moieties independently selected from the group consisting of halo, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, perhalo$(C_1\text{-}C_6)$alkyl, phenyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_1\text{-}C_{10})$heteroaryl, $(C_1\text{-}C_{10})$heterocyclic, formyl, -CN, $(C_1\text{-}C_6)$alkyl-(C=O)-, phenyl-(C=O)-, HO-(C=O)-, $(C_1\text{-}C_6)$alkyl-O-(C=O)-, $(C_1\text{-}C_6)$alkyl-NH-(C=O)-, $[(C_1\text{-}C_6)\text{alkyl}]_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[$((C_1\text{-}C_6)$alkyl)-N]-(C=O)-, $-NO_2$, amino, $(C_1\text{-}C_6)$alkylamino, $[(C_1\text{-}C_6)\text{alkyl}]_2$-amino, $(C_1\text{-}C_6)$alkyl-(C=O)-NH-, $(C_1\text{-}C_6)$alkyl-(C=O)-[$((C_1\text{-}C_6)$alkyl)-N]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[$((C_1\text{-}C_6)$alkyl)-N]-, H_2N-(C=O)-NH-, $(C_1\text{-}C_6)$alkyl-HN-(C=O)-NH-, $[(C_1\text{-}C_6)\text{alkyl-}]_2$N-(C=O)-NH-, $(C_1\text{-}C_6)$alkyl-HN-(C=O)-[$((C_1\text{-}C_6)$alkyl)-N]-, $[(C_1\text{-}C_6)\text{alkyl-}]_2$N-(C=O)-[$((C_1\text{-}C_6)$alkyl)-N]-, phenyl-HN-(C=O)-NH-, $(\text{phenyl-})_2$N-(C=O)-NH-, phenyl-HN-(C=O)-[$((C_1\text{-}C_6)$alkyl)-N]-, $(\text{phenyl-})_2$N-(C=O)-[$((C_1\text{-}C_6)$alkyl)-N]-, $(C_1\text{-}C_6)$alkyl-O-(C=O)-NH-, $(C_1\text{-}C_6)$alkyl-O-(C=O)-[$((C_1\text{-}C_6)$alkyl)-N]-, phenyl-O-(C=O)-NH-, phenyl-O-(C=O)-[$((C_1\text{-}C_6)$alkyl)-N]-, $(C_1\text{-}C_6)$alkyl-SO_2NH-, phenyl-SO_2NH-, $(C_1\text{-}C_6)$alkyl-SO_2-, phenyl-SO_2-, hydroxy, $(C_1\text{-}C_6)$alkoxy, perhalo$(C_1\text{-}C_6)$alkoxy, phenoxy, $(C_1\text{-}C_6)$alkyl-(C=O)-O-, phenyl-(C=O)-O-, H_2N-(C=O)-O-, $(C_1\text{-}C_6)$alkyl-HN-(C=O)-O-, $[(C_1\text{-}C_6)\text{alkyl-}]_2$N-(C=O)-O-, phenyl-HN-(C=O)-O-, and $(\text{phenyl-})_2$N-(C=O)-O-; wherein two adjacent R^2 substituents on said $(C_3\text{-}C_{10})$cycloalkyl, phenyl, $(C_1\text{-}C_{10})$heteroaryl or $(C_1\text{-}C_{10})$heterocyclic may be taken together with the carbon or heteroatom to which they are attached to form a five to six membered carbocyclic or heterocyclic ring; wherein each of said moieties containing a phenyl alternative may optionally be substituted by one or two radicals independently selected from the group consisting of $(C_1\text{-}C_6)$alkyl, halo, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl and perhalo$(C_1\text{-}C_6)$alkoxy;

each R^3 is independently selected from the group consisting of halo, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, perhalo$(C_1\text{-}C_6)$alkyl, phenyl, $(C_1\text{-}C_{10})$heteroaryl, $(C_1\text{-}C_{10})$heterocyclic, $(C_3\text{-}C_{10})$cycloalkyl, hydroxy, $(C_1\text{-}C_6)$alkoxy, perhalo$(C_1\text{-}C_6)$alkoxy, phenoxy, $(C_1\text{-}C_{10})$heteroaryl-O-, $(C_1\text{-}C_{10})$heterocyclic-O-, $(C_3\text{-}C_{10})$cycloalkyl-O-, $(C_1\text{-}C_6)$alkyl-S, $(C_1\text{-}C_6)$alkyl-SO_2-, $(C_1\text{-}C_6)$alkyl-NH-SO_2-, $-NO_2$, amino, $(C_1\text{-}C_6)$alkylamino, $[(C_1\text{-}C_6)\text{alkyl}]_2$-amino, $(C_1\text{-}C_6)$alkyl-SO_2-NH-, $(C_1\text{-}C_6)$alkyl-(C=O)-NH-, $(C_1\text{-}C_6)$alkyl-(C=O)-[$((C_1\text{-}C_6)$alkyl)-N]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[$((C_1\text{-}C_6)$alkyl)-N]-, -CN, $(C_1\text{-}C_6)$alkyl-(C=O)-, phenyl-(C=O)-, $(C_1\text{-}C_{10})$heteroaryl-(C=O)-, $(C_1\text{-}C_{10})$heterocyclic-(C=O)-, $(C_3\text{-}C_{10})$cycloalkyl-(C=O)-, HO-(C=O)-, $(C_1\text{-}C_6)$alkyl-O-(C=O)-, H_2N(C=O)-, $(C_1\text{-}C_6)$alkyl-NH-(C=O)-, $[(C_1\text{-}C_6)\text{alkyl}]_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[$((C_1\text{-}C_6)$alkyl)-N]-(C=O)-, $(C_1\text{-}C_{10})$heteroaryl-NH-(C=O)-, $(C_1\text{-}C_{10})$heterocyclic-NH-(C=O)-, $(C_3\text{-}C_{10})$cycloalkyl-NH-(C=O)- and $(C_1\text{-}C_6)$alkyl-(C=O)-O-; wherein two adjacent R^3 substituents may optionally be taken

together to form a three to six membered carbocyclic or heterocyclic ring;
s is an integer from zero to five;
R^4 and R^6 are each independently selected from the group consisting of hydrogen, halo and R^9-B-$(CH_2)_n$-;
n is an integer from zero to six;
each B is independently a bond, -(CHR^{10})-, -O-, -S-, -(SO_2)-, -(C=O)-, -O(C=O)-, -(C=O)-O-, -(C=O)-NR^{10}-, -$(R^{10}$-N)-, -$(R^{10}$-N)-SO_2-, -$(R^{10}$-N)-(C=O)-, -SO_2-(NR^{10})-, -$(R^{10}$-N)-(C=O)-(NR^{11})- -(O)-(C=O)-(NR^{10})- or -$(R^{10}$-N)-(C=O)-O-;
R^5 and R^7 are each independently selected from the group consisting of hydrogen, R^{14}-$(CR^{15}H)_p$-, phenyl, $(C_1$-$C_{10})$heteroaryl, $(C_1$-$C_{10})$heterocyclic, $(C_3$-$C_{10})$cycloalkyl, $(C_1$-$C_6)$alkyl-(SO_2)-, phenyl-(SO_2)-, H_2N-(SO_2)-, $(C_1$-$C_6)$alkyl-NH-(SO_2)-, $[(C_1$-$C_6)$alkyl-$]_2$N-(SO_2)-, phenyl-NH-(SO_2)-, (phenyl-$)_2$N-(SO_2)-, R^{16}-$(C_1$-$C_6)$ alkyl-(C=O)-, phenyl-(C=O)-, $(C_1$-$C_{10})$heteroaryl-(C=O)-, $(C_1$-$C_{10})$heterocyclic-(C=O)-, $(C_3$-$C_{10})$cycloalkyl-(C=O)-, $(C_1$-$C_6)$alkyl-O-(C=O)-, $(C_1$-$C_{10})$heterocyclic-O-(C=O)-, $(C_3$-$C_{10})$cycloalkyl-O-(C=O)-, H_2N-(C=O)-, $(C_1$-$C_6)$alkyl-NH-(C=O)-, phenyl-NH-(C=O)-, $(C_1$-$C_{10})$heteroaryl-NH-(C=O)-, $(C_1$-$C_{10})$heterocyclic-NH-(C=O)-, $(C_3$-$C_{10})$cycloalkyl-NH-(C=O)-, $[(C_1$-$C_6)$alkyl-$]_2$N-(C=O)-, (phenyl-$)_2$N-(C=O)-, phenyl-[$(C_1$-$C_6)$alkyl)-N]-(C=O)-, $(C_1$-$C_{10})$heteroaryl-[$(C_1$-$C_6)$alkyl)-N]-(C=O)-, $(C_1$-$C_{10})$heterocyclic-[$(C_1$-$C_6)$ alkyl)-N]-(C=O)-, and $(C_3$-$C_{10})$cycloalkyl-[$(C_1$-$C_6)$alkyl)-N]-(C=O)-, wherein each of the aforesaid phenyl, heterocyclic, heteroaryl or cycloalkyl R^5 and R^7 alternatives may optionally be independently substituted by one to four moieties independently selected from the group consisting of halo, R^{16}-$(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, perhalo$(C_1$-$C_6)$alkyl, $(C_3$-$C_{10})$cycloalkyl, phenyl, benzyl, $(C_1$-$C_{10})$heterocyclic, $(C_1$-$C_{10})$heteroaryl, $(C_1$-$C_6)$alkyl-SO_2-, formyl, -CN, $(C_1$-$C_6)$alkyl-(C=O)-, $(C_3$-$C_{10})$cycloalkyl-(C=O)-, phenyl-(C=O)-, $(C_1$-$C_{10})$heterocyclic-(C=O)-, $(C_1$-$C_{10})$heteroaryl-(C=O)-, HO-(C=O)-, $(C_1$-$C_6)$alkyl-O-(C=O)-, $(C_3$-$C_{10})$cycloalkyl-O-(C=O)-, $(C_1$-$C_{10})$heterocyclic-O-(C=O)-, $(C_1$-$C_6)$alkyl-NH-(C=O)-, $(C_3$-$C_{10})$cycloalkyl-NH-(C=O)-, phenyl-NH-(C=O)-, $(C_1$-$C_{10})$heterocyclic-NH-(C=O)-, $(C_1$-$C_{10})$heteroaryl-NH-(C=O)-, $[(C_1$-$C_6)$alkyl$]_2$-N-(C=O)-, phenyl-[$(C_1$-$C_6)$alkyl)-N]-(C=O)-, hydroxy, $(C_1$-$C_6)$alkoxy, perhalo$(C_1$-$C_6)$alkoxy, $(C_3$-$C_{10})$cycloalkyl-O-, phenoxy, $(C_1$-$C_{10})$heterocyclic-O-, $(C_1$-$C_{10})$heteroaryl-O-, $(C_1$-$C_6)$alkyl-(C=O)-O-, $(C_3$-$C_{10})$cycloalkyl-(C=O)-O-, phenyl-(C=O)-O-, $(C_1$-$C_{10})$heterocyclic-(C=O)-O-, $(C_1$-$C_{10})$heteroaryl-(C=O)-O-, -NO_2, amino, $(C_1$-$C_6)$alkylamino, $[(C_1$-$C_6)$alkyl$]_2$-amino, formamidyl, $(C_1$-$C_6)$alkyl-(C=O)-NH-, $(C_3$-$C_{10})$cycloalkyl-(C=O)-NH-, phenyl-(C=O)-NH-, $(C_1$-$C_{10})$heterocyclic-(C=O)-NH-, $(C_1$-$C_{10})$heteroaryl-(C=O)-NH-, $(C_1$-$C_6)$alkyl-(C=O)-[$(C_1$-$C_6)$alkyl)-N]-, phenyl-(C=O)-[$(C_1$-$C_6)$alkyl-N]-, $(C_1$-$C_6)$alkyl-SO_2NH-, $(C_3$-$C_{10})$cycloalkyl-SO_2NH-, phenyl-SO_2NH-, $(C_1$-$C_{10})$heterocyclic-SO_2NH- and $(C_1$-$C_{10})$heteroaryl-SO_2NH-; wherein each of said phenyl and heteroaryl moiety alternatives may optionally be substituted by one or two radicals independently selected from halo, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, perfluoro$(C_1$-$C_6)$alkyl and perfluoro$(C_1$-$C_6)$ alkoxy;
p is an integer from one to six;
R^9 is selected from the group consisting of hydrogen, -CF_3, -C≡N, R^{13}-$(R^{12}CH)_m$-, phenyl, $(C_1$-$C_{10})$heteroaryl, $(C_1$-$C_{10})$heterocyclic and $(C_3$-$C_{10})$cycloalkyl; wherein each of the aforesaid R^9 phenyl, $(C_1$-$C_{10})$heteroaryl, $(C_1$-$C_{10})$heterocyclic and $(C_3$-$C_{10})$cycloalkyl substituents may optionally be substituted by one to four moieties independently selected from the group consisting of halo, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, perhalo $(C_1$-$C_6)$alkyl, phenyl, $(C_1$-$C_{10})$heteroaryl, $(C_1$-$C_{10})$heterocyclic, $(C_3$-$C_{10})$cycloalkyl, hydroxy, $(C_1$-$C_6)$alkoxy, perhalo$(C_1$-$C_6)$alkoxy, phenoxy, $(C_1$-$C_{10})$heteroaryl-O-, $(C_1$-$C_{10})$heterocyclic-O-, $(C_3$-$C_{10})$cycloalkyl-O-, $(C_1$-$C_6)$alkyl-S-, $(C_1$-$C_6)$alkyl-SO_2-, $(C_1$-$C_6)$alkyl-NH-SO_2-, -NO_2, amino, $(C_1$-$C_6)$alkylamino, $[(C_1$-$C_6)$alkyl$]_2$-amino, $(C_1$-$C_6)$alkyl-SO_2-NH-, $(C_1$-$C_6)$alkyl-(C=O)-NH-, $(C_1$-$C_6)$alkyl-(C=O)-[$(C_1$-$C_6)$alkyl)-N]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[$(C_1$-$C_6)$alkyl)-N]-, -CN, $(C_1$-$C_6)$alkyl-(C=O)-, phenyl-(C=O)-, $(C_1$-$C_{10})$heteroaryl-(C=O)-, $(C_1$-$C_{10})$heterocyclic-(C=O)-, $(C_3$-$C_{10})$cycloalkyl-(C=O)-, HO-(C=O)-, $(C_1$-$C_6)$alkyl-O-(C=O)-, H_2N(C=O)-, $(C_1$-$C_6)$alkyl-NH-(C=O)-, $[(C_1$-$C_6)$alkyl$]_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[$(C_1$-$C_6)$alkyl)-N]-(C=O)-, $(C_1$-$C_{10})$heteroaryl-NH-(C=O)-, $(C_1$-$C_{10})$heterocyclic-NH-(C=O)-, $(C_3$-$C_{10})$cycloalkyl-NH-(C=O)-, $(C_1$-$C_6)$ alkyl-(C=O)-O- and phenyl-(C=O)-O-; wherein two adjacent moieties on said R^9 phenyl, $(C_1$-$C_{10})$heterocyclic or $(C_3$-$C_{10})$cycloalkyl substituents may be taken together with the carbon or heteroatom to which they are attached to form a five to six membered heterocyclic or carbocyclic ring;
m is an integer from one to six;
R^{10} is hydrogen, $(C_1$-$C_6)$alkyl-SO_2- or $(C_1$-$C_6)$alkyl;
R^{11} is hydrogen or $(C_1$-$C_6)$alkyl;
each R^{12} is independently selected from the group consisting of hydrogen, amino, $(C_1$-$C_6)$alkoxy or $(C_1$-$C_6)$ alkyl;
R^{13} is selected from the group consisting of hydrogen, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, phenyl, $(C_1$-$C_{10})$heteroaryl, $(C_1$-$C_{10})$heterocyclic, $(C_3$-$C_{10})$cycloalkyl, hydroxy, $(C_1$-$C_6)$alkoxy, p rhalo$(C_1$-$C_6)$alkoxy, phenoxy, $(C_1$-$C_{10})$heteroaryl-O-, $(C_1$-$C_{10})$heterocyclic-O-, $(C_3$-$C_{10})$cycloalkyl-O-, $(C_1$-$C_6)$alkyl-S-, $(C_1$-$C_6)$ alkyl-SO_2-, $(C_1$-$C_6)$alkyl-NH-SO_2-, -NO_2, amino, $(C_1$-$C_6)$alkylamino, $[(C_1$-$C_6)$alkyl$]_2$-amino, $(C_1$-$C_6)$alkyl-

SO_2-NH-, phenyl-SO_2-NH-, (C_1-C_6)alkyl-SO_2-[((C_1-C_6)alkyl)-N]-, phenyl-SO_2-[((C_1-C_6)alkyl)-N]-, (C_1-C_6)alkyl-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[((C_1-C_6)alkyl)-N]-, -CN, (C_1-C_6)alkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, (C_1-C_6)alkyl-(C=O)-O- and phenyl-(C=O)-O-;

R^{14} is selected from the group consisting of hydrogen, halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, phenyl, (C_1-C_{10})heterocyclic, (C_1-C_{10})heteroaryl, phenyl-(S=O)-, (C_1-C_6)alkyl-SO_2-, phenyl-SO_2-, H_2N-SO_2-, (C_1-C_6)alkyl-NH-SO_2-, phenyl-NH-SO_2-, [(C_1-C_6)alkyl-]$_2$N-SO_2-, (phenyl-)$_2$N-SO_2-, formyl, -CN, (C_1-C_6)alkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, HO-(C=O)-, R^{16}-(C_1-C_6)alkyl-O-(C=O)-, (C_3-C_{10})cycloalkyl-O-(C=O)-, (C_1-C_{10})heterocyclic-O-(C=O)-, H_2N-(C=O)-, R^{16}-(C_1-C_6)alkyl-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, phenyl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_1-C_{10})heteroaryl-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_1-C_{10})heterocyclic-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_3-C_{10})cycloalkyl[((C_1-C_6)alkyl)-N]-(C=O)-, hydroxy, R^{16}-(C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, (C_3-C_{10})cycloalkyl-O-, phenoxy, (C_1-C_{10})heterocyclic-O-, (C_1-C_{10})heteroaryl-O-, R^{16}-(C_1-C_6)alkyl-(C=O)-O-, (C_3-C_{10})cycloalkyl-(C=O)-O-, phenyl-(C=O)-O-, (C_1-C_{10})heterocyclic-(C=O)-O-, (C_1-C_{10})heteroaryl-(C=O)-O-, -NO_2, amino, R^{16}-(C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, formamidyl, R^{16}-(C_1-C_6)alkyl-(C=O)-NH-, (C_3-C_{10})cycloalkyl-(C=O)-NH-, phenyl-(C=O)-NH-, (C_1-C_{10})heterocyclic-(C=O)-NH-, (C_1-C_{10})heteroaryl-(C=O)-NH-, R^{16}-(C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-[((C_1-C_6)alkyl)-N]-, R^{16}-(C_1-C_6)alkyl-SO_2NH-, (C_3-C_{10})cycloalkyl-SO_2NH-, phenyl-SO_2NH-, (C_1-C_{10})heterocyclic-SO_2NH- and (C_1-C_{10})heteroaryl-SO_2NH-; wherein each of the aforesaid phenyl, heterocyclic, heteroaryl or cycloalkyl R^{14} alternatives may optionally be independently substituted by one to four moieties independently selected from the group consisting of halo, R^{16}-(C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, phenyl, benzyl, (C_1-C_{10})heterocyclic, (C_1-C_{10})heteroaryl, (C_1-C_6)alkyl-SO_2-, formyl, -CN, R^{16}-(C_1-C_6)alkyl-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, (C_3-C_{10})cycloalkyl-O-(C=O)-, (C_1-C_{10})heterocyclic-O-(C=O)-, (C_1-C_{10})heteroaryl-O-(C=O)-, H_2N-(C=O)-, R^{16}-(C_1-C_6)alkyl-NH-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, phenyl-NH-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, hydroxy, R^{16}-(C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, (C_3-C_{10})cycloalkyl-O-, phenoxy, (C_1-C_{10})heterocyclic-O-, (C_1-C_{10})heteroaryl-O-, R^{16}-(C_1-C_6)alkyl-(C=O)-O-, (C_3-C_{10})cycloalkyl-(C=O)-O-, phenyl-(C=O)-O-, (C_1-C_{10})heterocyclic-(C=O)-O-, (C_1-C_{10})heteroaryl-(C=O)-O-, -NO_2, amino, R^{16}-(C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, formamidyl, R^{16}-(C_1-C_6)alkyl-(C=O)-NH-, (C_3-C_{10})cycloalkyl-(C=O)-NH-, phenyl-(C=O)-NH-, (C_1-C_{10})heterocyclic-(C=O)-NH-, (C_1-C_{10})heteroaryl-(C=O)-NH-, R^{16}-(C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-[((C_1-C_6)alkyl)-N]-, R^{16}-(C_1-C_6)alkyl-SO_2NH-, (C_3-C_{10})cycloalkyl-SO_2NH-, phenyl-SO_2NH-, (C_1-C_{10})heterocyclic-SO_2NH- and (C_1-C_{10})heteroaryl-SO_2NH-; wherein each of said phenyl and heteroaryl moiety alternatives may optionally be substituted by one or two radicals independently selected from the group consisting of halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, perfluoro(C_1-C_6)alkyl and perfluoro(C_1-C_6)alkoxy;

each R^{15} is independently selected from the group consisting of hydrogen, halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, perhalo(C_1-C_6)alkyl, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkyl-(C=O)-O-, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, formamidyl and (C_1-C_6)alkyl-(C=O)-NH-;

each R^{16} is independently selected from the group consisting of hydrogen, halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, perhalo(C_1-C_6)alkyl, (C_1-C_{10})heterocyclic, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, hydroxy, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkoxy, (C_1-C_6)alkyl-(C=O)-O-, -NO_2, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, formamidyl and (C_1-C_6)alkyl-(C=O)-NH-; wherein said (C_1-C_{10})heterocyclic may optionally be substituted by one to three substituents independently selected from the group consisting of halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, amino, (C_1-C_6)alkylamino and [(C_1-C_6)alkyl]$_2$-amino;

or R^4 and R^6 or R^4 and R^7 or R^5 and R^6 may be taken together with the atoms to which they are attached to form an optionally substituted five to ten membered saturated, unsaturated or aromatic ring optionally containing two to three heteroatoms independently selected from NH, N, O, S, SO or SO_2; wherein said ring may be optionally substituted by one to three substituents independently selected from the group consisting of oxo, halo, (C_1-C_6)alkyl, phenyl, (C_1-C_{10})heteroaryl, (C_1-C_{10})heterocyclic, (C_3-C_{10})cycloalkyl, hydroxy, (C_1-C_6)alkoxy, phenoxy, (C_1-C_{10})heteroaryl-O-, (C_1-C_{10})heterocyclic-O-, (C_3-C_{10})cycloalkyl-O-, (C_1-C_6)alkyl-S-, (C_1-C_6)alkyl-SO_2-, phenyl-S-, phenyl-(S=O)-, phenyl-SO_2-, (C_1-C_6)alkyl-NH-SO_2-, [(C_1-C_6)alkyl]$_2$-N-SO_2-,

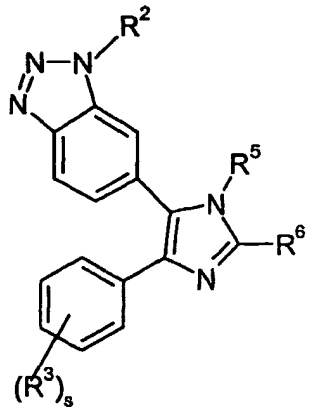
phenyl-NH-SO_2-, (phenyl)$_2$-N-SO_2-, phenyl-[N(C_1-C_6)alkyl]-SO_2-, formyl, (C_1-C_6)alkyl-(C=O)-, phenyl-(C=O)-, (C_1-C_{10})heteroaryl-(C=O)-, (C_1-C_{10})heterocyclic-(C=O)-, (C_3-C_{10})cycloalkyl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, (C_1-C_{10})heterocyclic-O-(C=O)-, (C_3-C_{10})cycloalkyl-O-(C=O)-, H_2N-(C=O)-, (C_1-C_6)alkyl-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, phenyl-NH-(C=O)-, phenyl-[(C_1-C_6)alkyl)-N]-(C=O)-, (C_1-C_{10})heteroaryl-NH-(C=O)-, (C_1-C_{10})heteroaryl-[(C_1-C_6)alkyl)-N]-(C=O)-, (C_1-C_{10})heterocyclic-NH-(C=O)-, (C_1-C_{10})heterocyclic-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_3-C_{10})cycloalkyl-NH-(C=O)-, (C_3-C_{10})cycloalkyl-[((C_1-C_6)alkyl)-N]-(C=O)-, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$amino, (C_1-C_6)alkyl-SO_2-NH-, phenyl-SO_2-NH-, (C_1-C_6)alkyl-SO_2-[((C_1-C_6)alkyl)-N]-, phenyl-SO_2-[((C_1-C_6)alkyl)-N]-, formamidyl, (C_1-C_6)alkyl-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-(C=O)-NH-, phenyl-(C=O)-[((C_1-C_6)alkyl)-N]-, (C_1-C_{10})heteroaryl-(C=O)-NH-, (C_1-C_{10})heteroaryl-(C=O)-[((C_1-C_6)alkyl)-N]-, (C_1-C_{10})heterocyclic-(C=O)-NH-, (C_1-C_{10})heterocyclic-(C=O)-[((C_1-C_6)alkyl)-N]-, (C_3-C_{10})cycloalkyl-(C=O)-NH-, (C_3-C_{10})cycloalkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, H_2N(C=O)-NH-, (C_1-C_6)alkyl-HN-(C=O)-NH-, (C_1-C_6)alkyl-HN-(C=O)-[((C_1-C_6)alkyl)-N]-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-NH-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-[((C_1-C_6)alkyl)-N]-, phenyl-HN-(C=O)-NH-, phenyl-HN-(C=O)-[((C_1-C_6)alkyl)-N]-, (phenyl)$_2$-N-(C=O)-NH-, (phenyl)$_2$-N-(C=O)-[((C_1-C_6)alkyl)-N]-, (C_1-C_{10})heteroaryl-HN-(C=O)-NH-, (C_1-C_{10})heteroaryl-HN-(C=O)-[((C_1-C_6)alkyl)-N]-, [(C_1-C_{10})heteroaryl]$_2$-N-(C=O)-[((C_1-C_6)alkyl)-N]-, [(C_1-C_{10})heteroaryl]$_2$-N-(C=O)-NH-, (C_1-C_{10})heterocyclic-HN-(C=O)-NH-, (C_1-C_{10})heterocyclic-HN-(C=O)-[((C_1-C_6)alkyl)-N]-, [(C_1-C_{10})heterocyclic]$_2$-N-(C=O)-[((C_1-C_6)alkyl)-N]-, [(C_1-C_{10})heterocyclic]$_2$-N-(C=O)-NH-, (C_3-C_{10})cycloalkyl-HN-(C=O)-NH-, (C_3-C_{10})cycloalkyl-HN-(C=O)-[((C_1-C_6)alkyl)-N]-, [(C_3-C_{10})cycloalkyl]$_2$-N-(C=O)-[((C_1-C_6)alkyl)-N]-, [(C_3-C_{10})cycloalkyl]$_2$-N-(C=O)-NH-, (C_1-C_6)alkyl-(C=O)-O-, phenyl-(C=O)-O-, (C_1-C_{10})heteroaryl-(C=O)-O-, (C_1-C_{10})heterocyclic-(C=O)-O-, (C_3-C_{10})cycloalkyl-(C=O)-O-, (C_1-C_6)alkyl-NH-(C=O)-O-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-O-, phenyl-NH-(C=O)-O-, (C_1-C_{10})heteroaryl-NH-(C=O)-O-, (C_1-C_{10})heterocyclic-NH-(C=O)-O- and (C_3-C_{10})cycloalkyl-NH-(C=O)-O-;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R^2 is optionally substituted (C_1-C_6)alkyl, phenyl, (C_3-C_{10})cycloalkyl, (C_1-C_{10})heteroaryl or (C_1-C_{10})heterocyclic.

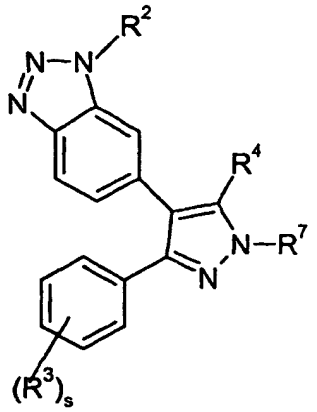
3. A compound according to claim 1 wherein R^2 is (C_1-C_6)alkyl, optionally substituted with one to four groups independently selected from halo, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkoxy, perhalo(C_1-C_6)alkyl, perhalo(C_1-C_6)alkoxy, -CN, -NO_2, amino, (C_1-C_6)alkylamino, [(C_1-C_6)alkyl]$_2$-amino, HO-(C=O)-, (C_1-C_6)alkyl-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, (C_1-C_6)alkyl-CO_2-, (C_1-C_6)alkyl-(C=O)-NH-, (C_1-C_6)alkyl-NH-(C=O)-, (C_1-C_6)alkyl-(C=O)-[((C_1-C_6)alkyl)-N]-, (C_1-C_6)alkyl-[((C_1-C_6)alkyl)-N]-(C=O)-, (C_1-C_6)alkyl-SO_2NH-, (C_1-C_6)alkyl-SO_2-, optionally substituted phenyl-(C=O)-, optionally substituted phenyl-(C=O)-O-, optionally substituted phenoxy, optionally substituted phenyl-NH-(C=O)-, optionally substituted phenyl-[((C_1-C_6)alkyl)-N]-(C=O)-, optionally substituted phenyl-(C=O)-NH- and optionally substituted phenyl-(C=O)-[((C_1-C_6)alkyl)-N]-.

4. A compound according to claim 1, wherein the compound has the formula



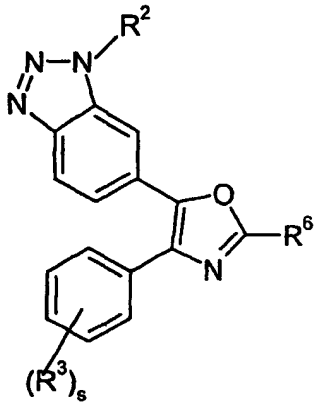
I(b)

5. A compound according to claim 1, wherein the compound has the formula



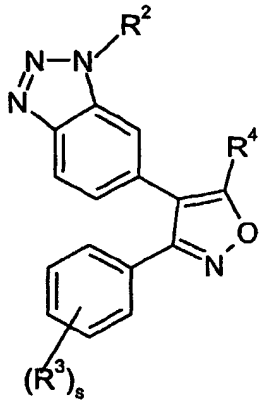
I(c)

6. A compound according to claim 1, wherein the compound has the formula



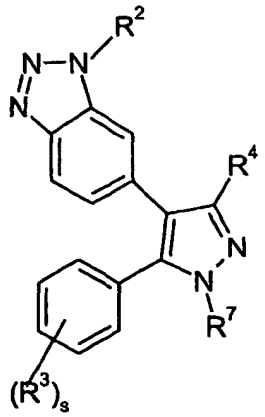
I(d)

7. A compound according to claim 1, wherein the compound has the formula



I(e)

8. A compound according to claim 1, wherein the compound has the formula



I(f)

9. A compound according to claim 1, wherein R^4 is hydrogen.

10. A compound according to claim 1, wherein R^7 is selected from the group consisting of hydrogen and optionally substituted phenyl, $(C_1\text{-}C_{10})$heteroaryl, $(C_1\text{-}C_{10})$heterocyclic and $(C_3\text{-}C_{10})$cycloalkyl.

11. A compound according to any of the preceding claims, wherein s is an integer from zero to four and each R^3 is independently selected from the group consisting of halo, -CN, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl and perhalo$(C_1\text{-}C_6)$alkyl.

12. A compound according to claim 1, wherein said compound is selected from the group consisting of:

6-[5-(4-fluoro-3-methyl-phenyl)-3H-imidazol-4-yl]-1-isopropyl-1H-benzotriazole;
6-[4-(4-fluoro-phenyl)-oxazol-5-yl]-1-isopropyl-1H-benzotriazole;
6-[5-(4-fluoro-phenyl)-3H-imidazol-4-yl]-1-isopropyl-1H-benzotriazole;
6-[4-(4-fluoro-3-methyl-phenyl)-oxazol-5-yl]-1-isopropyl-1H-benzotriazole;
6-[4-(4-Fluoro-phenyl)-oxazol-5-yl]-1-isopropyl-1H-benzotriazole;
1-isopropyl-6-(5-phenyl-3H-imidazol-4-yl)-1H-benzotriazole;
1-isopropyl-6-(4-phenyl-oxazol-5-yl)-1H-benzotriazole;
6-[5-(4-fluoro-3-methyl-phenyl)-3H-im idazol-4-yl]-1-methyl-1H-benzotriazole;
6-[5-(4-fluoro-phenyl)-2-pyridin-3-yl-3H-imidazol-4-yl]-1-isopropyl-1H-benzotriazole; and
6-[5-(4-fluoro-phenyl)-2-pyrazin-2-yl-3H-imidazol-4-yl]-1-isopropyl-1H-benzotriazole.

13. A compound according to any of the preceding claims for use as a medicament.

14. Use of a compound according to any of claims 12 to 13 for the manufacture of a medicament for the treatment of an ERK/MAP kinase mediated disease in a mammal.

15. Use according to claim 14, wherein the disease is selected from psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, Alzheimer's disease, stroke, ischemic and hemorrhagic stroke, neurotrauma/closed head injury, asthma, adult respiratory distress syndrome, chronic obstructive pulmonary disease, cerebral malaria, meningitis, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcostosis, bone resorption disease, osteoporosis, restenosis, cardiac reperfusion injury, brain and renal reperfusion injury, chronic renal failure, thrombosis, glomerularonephritis, diabetes, diabetic retinopathy, macular degeneration, graft vs. host reaction, allograft rejection, inflammatory bowel disease, Crohn's disease, ulcerative colitis, neurodegenerative disease, multiple sclerosis, muscle degeneration, diabetic retinopathy, macular degeneration, tumor growth and metastasis, angiogenic disease, rhinovirus infection, peroral disease, such as gingivitis and periodontitis, eczema, contact dermatitis, psoriasis, sunburn, and conjunctivitis.

16. A pharmaceutical composition for the treatment of an ERK/MAP kinase mediated disease in a mammal which

comprises an effective amount of a compound according to any of claims 1 to 12 and a pharmaceutically acceptable carrier.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 02 25 2153

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C07D
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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	26 July 2002	Schmid, A

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